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AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

ENTERED AS SECOND-CLASS MATTER, JANUARY 23, 1909, AT THE POSTOFFICE AT CHICAGO, ILLINOIS, UNDER ACT OF CONGRESS OF MARCH 3, 1879

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The Archives of Internal Medicine

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A NOTE REGARDING MYIASIS, ESPECIALLY THAT DUE TO SYRPHID LARVAE*

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DETROIT

Bruce[1] (1917) has recently published a paper reporting from Vancouver Island a very interesting case of vaginal myiasis in the cow due to the "rat-tailed larva" of the drone fly, *Eristalis*. He does not say how many larva were found, but notes that the vagina was diseased and that a discharge was present. In his paper, Bruce says: "I am unable to find any reference to invasion of the vaginal cavity by the larvae of *E. tenax* in either man or animals." As a matter of fact, Bruce's case is the second recorded case of this sort, the first having been published by Hall and Muir[2] (1913). Their record is as follows:

> In the Bureau of Animal Industry collection of parasites . . . there are also eight *Eristalis* larvae sent in from Laurel, Md., in 1909, with the statement that they were passed in a jelly-like substance from the vagina of cattle. In correspondence relative to these specimens, Dr. B. H. Ransom suggests to the sender:
>
> Probably a diseased condition of the organ in which you found these larvae created an odor which attracted the flies to this particular place, with the result that they have deposited their young in the unusual location.

The above record has been cited by Metcalf[3] (1916), but it is not at all surprising that the record escaped the attention of Dr. Bruce. The fact that we now have two records of the presence of *Eristalis* larvae in the diseased vagina of cattle instead of one record, however, does much to establish the validity of both records and the likelihood that similar occurrences do happen from time to time.

Hall and Muir[2] listed a summary of seven published cases of myiasis in man due to larvae of the *Syrphidae*. To this they add their new case and four cases from the files of the United States Bureau of Entomology, furnished through the courtesy of Dr. L. O. Howard and

* Submitted for publication Oct. 23, 1917.

1. Bruce, E. A.: A New Parasite for Cattle. The Larvae of *Eristalis tenax L.* (drone fly), Jour. Am. Vet. Med. Assn., 1917, **1**, 66-68, Fig. 1.
2. Hall, M. C., and Muir, J. T.: A Critical Study of a Case of Myiasis Due to *Eristalis*, THE ARCHIVES INT. MED., 1913, **11**, 193.
3. Metcalf, C. L.: Syrphidae of Maine, Bull. 255, Maine Agric. Exper. Sta., 1916.

Mr. R. S. Clifton, and one from the files of the United States Bureau of Animal Industry, furnished through the courtesy of Dr. A. D. Melvin and Dr. B. H. Ransom, to whose courtesy they were also indebted for the record of the case of vaginal myiasis. Twelve of these were cases of gastro-intestinal myiasis and one (Leidy's) a case of nasal myiasis. To the summary of human cases by Hall and Muir, I wish to add an unpublished case in man, for which I am indebted to the kindness of Dr. Allen J. Smith of the University of Pennsylvania and Dr. F. J. Bardwell of Tunkhannock, Pa., and to note a subsequently published record by Iches[4] (1914), and three records of Austen (1912, not available), cited by Graham-Smith[5] (1914).

Under date of April 24, 1913, Dr. Smith wrote me as follows:

I have recorded here in our laboratory reports a case of *Eristalis* in the human stool, definitely regarded as *Eristalis*, and tentatively, for the same reason you assign in your case, *E. tenax* (common occurrence of the fly). The specimens (two) were sent Sept. 9, 1908, by Dr. F. J. Bardwell of Tunkhannock, Pa., through the State Health Department (the bacteriological work of which was then done by this laboratory) as from the stool of B. L., white, male, native, aged 18. No statement as to the condition of the subject and no account of the circumstances of recovery of the specimens were given, although doubtless Dr. Bardwell can furnish them. I note the specimens as 13 and 14 mm. in length, respectively, 4 and 5 mm. thick in anterior part; the "tail" as equaling the body length in the first, somewhat retracted in the second; tail curved anteriorly. Dark brown, firm, apparently brittle, seven pairs of hook-bearing prolegs (numerous hooks arranged in curved rows). Dorsally at head end two pairs of hooks, the posterior the longer and directed forward, the anterior the smaller and directed backward. On each side submedian row of indefinite tubercles, between which are a number of fine transverse ridges of the cuticle. Indefinitely seven-segmented. . . . It has never been published.

In response to a recent request for information in regard to this case, Dr. Bardwell wrote me, under date of Oct. 12, 1917, as follows:

I remember the case you refer to very well. . . . About a year after that, he had the same thing again. There is no doubt about it being a genuine case. Creolin, one dram to quart of hot water, was the treatment. The symptoms are intense irritation of the rectum.

Iches[4] (1914) states that when traveling in the Argentine Republic he found in the entomologic collection which is under Dr. Lahille's supervision, two rat-tailed larvae collected at Necochea in 1904, and was furnished the following history by Dr. Lahille:

A physician at Necochea was called in to attend a 7-year-old girl who complained of a pain in the rectum. Nothing was detected on simple examination and the doctor ordered washing, which brought about no change. He then gave a purgative, which caused the expulsion of the larvae, which were sent

4. Iches, L.: Un cas original d'hospitalisation rectale, Arch. d. parasitol., 1914, **3**, 473.

5. Graham-Smith, G. S.: Flies in Relation to Disease. Non-bloodsucking Flies. Cambridge, 1914.

to Lahille. The two larvae measured as follows: Body 12.5 mm. long by 2 mm. wide; tail 18 mm.; body 11 mm. long by 2 mm. wide; tail 13.5 mm. The color was dirty gray.

Austen's cases of human myiasis due to syrphid larvae are noted by Graham-Smith[5] as follows: "In England, Austen (1912) has met with . . . two cases due to the larvae of a *Syrphus* or hover-fly, one case due to the 'rat-tailed maggot' of *Eristalis tenax*. . . ."

It would appear, then, that there are at least seventeen records claiming the presence of syrphid larvae in the digestive tract of man; one record claiming their presence in the nostrils of man; and two records claiming their presence in the diseased vagina of cattle.

In passing, it might be noted that Blundeville in his book, "The Order of Curing Horse Diseases," published in 1609, says that a "bottee" has a "great head and small long tail like a needle." This is a very poor description of a bot and a fairly accurate description of a rat-tailed larva. It suggests that Blundeville had seen rat-tailed larvae in horse manure, a favorite breeding place, and regarded them as bots which had been passed by the horse, and this may be a rather common error. It is still a common error to regard free-living forms occurring in feces as parasites which have passed from the digestive tract. Herms[6] (1915) says that the frequency with which the larvae occur in liquid excrement must lead to caution in accepting reports that they have been evacuated, and adds: "The writer has on several occasions received specimens of 'rat-tailed' larvae which were said to have been evacuated by the 'double handful' and that the patient had 'steadily improved' thereafter."

As regards the species of syrphid involved in these cases, we may quote Metcalf's opinion:

> I wish to emphasize the practical impossibility, at our present state of published knowledge, of referring larvae found in such circumstances to a definite species, or even to the genus, unless specimens are reared to the adult. It seems to be the custom to refer any rat-tailed larva to *Eristalis tenax*, or at least to the genus *Eristalis*. Such records, unless based on adults reared from the larvae, must, it seems to me, be discarded as of no specific importance. I . . . have examined a dozen species of rat-tailed larvae belonging to several genera, the separation of which is exceedingly puzzling and difficult, and any one of which might easily be mistaken for the larvae of *Eristalis tenax*.

Hall and Muir[2] stated in regard to these rat-tailed larvae: "Only an occasional pupa, and never a larva, survives the winter." Regarding this point, Mr. E. R. Warren of Colorado Springs, Colo., a well-known ornithologist and mammalogist, wrote me, under date of March 18, 1913, as follows:

> The latter part of February, 1902, I took from an outdoor tank at a fish hatchery near Crested Butte, Colo., a bunch of live rat-tailed maggots, which were identified by Dr. L. O. Howard as *Eristalis tenax*. He made no com-

6. Herms, W. B.: Medical and Veterinary Entomology. New York, 1915.

ment as to the season when they were found, and perhaps did not understand that they were taken in winter. . . .

The tank was a wooden affair, perhaps 4 by 8 by 3 feet deep, in open air, not used for any special purpose, but the water from the hatchery flowed through it. This water is taken from a spring and piped right into the building and flows through the hatching troughs, and hence out into the tank I have mentioned. . . . As the winters are cold there, 9,000 feet, the temperature of the water in the tank was probably not much above 32 F., but as it comes from the spring into the hatchery it is 45 F. the year around.

One sort of myiasis about which little of a specific sort seems to be published is rectal myiasis, due to blow-fly larvae, especially in sick and in moribund animals, and more especially where there is blood in the feces. I have seen a few cases of this sort and had one case in the dog recently. In this case the dog was being used to determine the lethal dose of an anthelmintic, and a resultant hemorrhagic gastritis was the source of the blood in the feces. The day before this dog died, maggots were found to be crawling in and out of the anus. To alleviate this condition, the dog was given a rectal injection of 1 c.c. of chloroform in 9 c.c. of castor oil. On postmortem examination the following day, the rectum, colon and anal region were found free from larvae, but four larvae, dead when collected, were found in the small intestine. It is possible that these four larvae had been driven back up the large intestine by the rectal injection and had entered the small intestine either before or after the death of the dog. The dog had eaten nothing for several days, except a small amount of milk, and it appears more likely in this case that the larvae in the small intestine entered the body by way of the anus than by way of the mouth. It suggests that occasional cases of gastric and enteric myiasis might be explained in this way in cases in which the evidence seemed opposed to the idea of infection by mouth. Graham-Smith[5] (1914) has noted this as a possible mode of infection in man. He says that "Babies left exposed in an uncleanly condition may become infested. The larvae on hatching make their way into the rectum, and perhaps penetrate into the intestine."

A COMPARISON OF THE FUNCTIONAL AND ANATOMIC FINDINGS IN A SERIES OF CASES OF RENAL DISEASE*

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AND
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It is our purpose in this article to report a group of thirty cases of renal disease which have been studied by certain of the recently introduced methods of renal functional testing, including the estimation of the plasma chlorids. Fifteen of these cases have come to necropsy, thus affording an opportunity of comparing the functional and anatomic findings. The cases are classified into four main groups, with a few additional miscellaneous cases. The important clinical findings and the results of the functional tests are tabulated in Table 1. The pathology of the kidneys from the cases coming to necropsy is tabulated in Table 2. A general discussion of the findings in each group is given in the text. Detailed protocols of the individual cases are appended at the end of the report.

METHODS

Blood pressures were read by the auscultatory method, the diastolic pressure being read at the end of the fourth phase. The phenolsulphonephthalein figures represent in all cases the output in two hours after injection, allowing in the case of intramuscular injection an additional ten minutes for the appearance of the drug. Catheterization was not employed routinely but only when there was evidence of retention. The drug was injected into the lumbar muscles, as a rule, unless there was edema; in such cases it was given intravenously. Blood for chemical study was taken from the vein at the elbow either before breakfast or four hours after a light breakfast. For the estimation of the plasma chlorids and of plasma bicarbonate the blood was drawn directly into centrifuge tubes containing potassium oxalate crystals beneath paraffin oil and immediately centrifuged and the plasma pipetted from the cells. Blood urea nitrogen was determined by the method of Van Slyke and Cullen;[1] total nonprotein nitrogen by the method of Folin and Denis,[2] using titration instead of

* Submitted for publication Oct. 18, 1917.

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1. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea. Jour. Biol. Chem., 1914, **19,** 211.

2. Folin, O., and Denis, W.: New Methods for Determination of Total Nonprotein Nitrogen, Urea and Ammonia in Blood. Jour. Biol. Chem., 1912, **11,** 527.

nesslerization; plasma chlorids by the method of McLean and Van Slyke;[3] plasma bicarbonates by the method of Van Slyke.[4] In all cases the figures for the phenolsulphonephthalein test represent percentile excretion for two hours; for the blood urea nitrogen and total nonprotein nitrogen, milligrams of nitrogen per 100 c.c. of blood; for the plasma chlorids, grams of sodium chlorid per liter of plasma; for the plasma bicarbonate cubic centimeters of carbon dioxid gas per 100 c.c. of plasma reduced to 0 C. 760 mm. Hg, and corrected for vapor tension. The pathologic histology is based on tissues fixed either in Zenker's or Orth's fluid, sectioned in paraffin and stained with hematoxylin and eosin.

Acute Glomerulonephritis and Early Chronic Nephritis. — The series includes two cases of acute glomerulonephritis (Cases 1 and 2); one fatal, with necropsy, one with recovery. Both cases exhibited elevation of blood pressure, increase of the urea or nonprotein nitrogen of the blood, marked increase of the plasma chlorids and a reduction of the plasma bicarbonates. The pathology in Case 1 was that of an acute glomerulonephritis and acute suppurative interstitial nephritis.

Case 3 was one of early chronic nephritis with a tendency to recurring acute attacks. The renal functional tests in this case were normal at the time investigated. The nephritis in this case appeared to be secondary to acute throat infections.

Chronic Glomerulonephritis.—Eight cases are in the series (Cases 4 to 11) with six deaths and five necropsies. These cases show elevation of blood pressure, marked reduction in phenolsulphonephthalein excretion, very high blood urea or nonprotein nitrogen, fixation of the specific gravity of the urine and usually an albuminuric retinitis.

Certain features deserve comment. The frequency of either abdominal or lumbar pain, dull and aching in character, as one of the first symptoms observed in these cases is quite striking and has not, we believe, been sufficiently emphasized. The reduction in the plasma bicarbonates has been noted before by us[5] as a practically constant feature of this type of nephritis in the final stage. In Case 5 a considerable elevation of the plasma bicarbonates was secured by persistent alkaline therapy, but without any beneficial effect on the patient, as far as could be determined. It seems probable that the acidosis is without any serious effect per se on the patient; certainly, at least, any deleterious effect it may have is so overshadowed by graver disturbances as to be scarcely recognizable.

Of special interest are the kidneys with respect to the plasma chlorids in these patients. In contradistinction to the tendency in acute

3. McLean, F. C., and Van Slyke, D. D.: A Method for the Determination of Chlorids in Small Amounts of Body Fluids. Jour. Biol. Chem., 1915, **21,** 361.

4. Van Slyke, D. D.: A Method for the Determination of Carbon Dioxid and Carbonates in Solution. Jour. Biol. Chem., 1917, **30,** 347.

5. Austin, J. H., and Jonas, L.: Chemical Studies of Acidosis. Am. Jour. Med. Sc., 1917, **153,** 81.

glomerulonephritis, and indeed, in practically all the other forms of renal disease which we have thus far studied, the plasma chlorids are found to be low rather than high.. Cases 4 and 10 are within normal limits. Case 6 showed a very low figure. Whether the venesection and introduction of normal saline intravenously twelve hours before may have influenced this latter reading we are not prepared to say, but it cannot, we feel sure, wholly account for the low reading. In Case 5, although the first reading was elevated above the normal, the two subsequent readings were normal and the final reading very low. The patient had been kept on a salt-free diet, and this may have favored the reduction in the figure for the plasma chlorids, but does not wholly explain it, for in other forms of nephritis, and, as we have shown elsewhere,[6] in the normal dog it is impossible to produce such a reduction in the plasma chlorids by witholding salt with or without the free administration, by mouth, of distilled water. It seems fair to conclude, therefore, that in the last stage of glomerulonephritis, when the elevation of blood urea is the highest observed, there is a tendency to an absence of increase or to an actual reduction below normal of the plasma chlorids. The blood pressure falls in all cases shortly before death, but we were surprised to find that throughout the series the drop in the systolic and diastolic pressures was proportional, so that the ratio of the diastolic to the systolic pressure remains practically unchanged. We would have expected the fall to occur chiefly in the systolic pressure, but this appears not to be the case.

The pathology in all these cases is essentially the same, namely, a glomerulonephritis, with marked cellular proliferation in the tufts and with a variable degree of secondary fibrosis. No close parallel can be drawn between the clinical findings and the extent to which the secondary fibrosis of the glomeruli has occurred. In Cases 10 and 11 this was very marked. In Case 7 it has proceeded to only a very slight extent; in Case 9 the glomerular change was less definitely of the proliferative type and was largely one of hyalinization. It is interesting to note that this is the one case of the group coming to necropsy which did not show a very high blood pressure. All these cases showed more or less sclerosis of the renal vessels and interstitial fibrosis in the medulla and to some extent in the cortex. In the latter the fibrosis is always most marked about the obliterated glomeruli; areas in which the tubules belonging to the glomeruli have undergone collapse with atrophy of their epithelium and sometimes with practically complete obliteration.

Grossly, in all of these cases the kidney was contracted and usually pale in color.

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6. Austin, J. H., and Jonas, L.: Effects of Diet on the Plasma Chlorids and Chlorid Excretion in the Dog, Jour. Biol. Chem., 1918, **33**, 91.

These typical cases constitute a well marked group both clinically and in the histology of the kidney, and the condition deserves the specific name of chronic glomerulonephritis; for, although in the final stages there is extensive destruction of those tubules associated with the most diseased glomeruli, this destruction is clearly secondary to the primary disease of the glomeruli. There are good grounds for the view that while the elevation of the blood pressure in these cases is related to the primary glomerular disease, the reduction in the phenolsulphonephthalein output, the retention of the nitrogenous substances in the blood and the fixation of the specific gravity of the urine are consequent on the gradual secondary destruction of the tubules. McNider's[7] studies of the spontaneous glomerulonephritis of the dog, we believe, support this view. Clinically, we have observed repeatedly in these cases the early appearance of hypertension and the gradual development much later of the impaired renal functional tests.

Chronic Diffuse Nephritis.—In this group, which is substantially a mixed glomerular and tubular nephritis, we have included four cases (12 to 15) which exhibited one or more of the following: edema of the face, waxy pallor, large amounts of albumin in the urine, abundant casts of all kinds, doubly refractile lipoids in the urine, and relatively slight elevation of blood pressure. Because of the conspicuous presence of some of these features these cases should doubtless be included in the group of conditions variously called parenchymatous nephritis, tubular or degenerative nephritis, nephropathy or nephrosis. Careful study of the cases in this group either clinically or as regards the histology of the kidney in the two cases necropsied shows, however, that these cases merge with those of the previous group. The blood pressure in all was at some time more or less elevated, and in Case 12 was quite high. The albuminuria was in no case greater than in Case 11 of the other group. Casts were scanty in some cases and sometimes absent in others; in no case were they more abundant or more varied in character than in Cases 9 and 11 of the other group. The phenolsulphonephthalein test was, at least at the earlier examinations, higher in these cases than in the other group, but this is in part a matter of the stage of the case, for in both Cases 14 and 15 the phenolsulphonephthalein became very low before death, and in Case 7 of the other group the phenolsulphonephthalein was quite fair when first seen, two months before death. The difference in the elevation of the blood nitrogen in the two groups is one of degree only, and like the phenolsulphonephthalein probably much influenced by the stage of the disease. The plasma chlorids, however, in the cases studied, were

7. MacNider, W. de B.: A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog. Jour. Med. Research, 1916, **34**, 177.

higher than normal instead of normal or low, as in the other group, and from a recent case we know they may persist above normal until death.

In the other group it is worth noting, however, that the patient in Case 5, who exhibited eventually such a low plasma chlorid, had a high plasma chlorid when first seen five weeks earlier. The urinary specific gravity tends to approach fixation at about 1.011 to 1.013, although this is less pronounced than in the other group. In studying the pathology we find no sharp distinction between the two groups in the gross pathology. Histologically, it is undoubtedly true that both cases in this group exhibited more evidence of disease or destruction of the tubular epithelium than has occurred in the cases of the other group. This was conspicuous, however, only in Case 15. On the other hand, both cases in this group exhibited definite destruction of the glomeruli; in Case 14, indistinguishable in character from that seen in the other group. It is true that both cases, and especially Case 15, exhibited less evidence of cellular proliferation in the glomerular tufts than did most of the cases in the other group, the lesions being more in the nature of a hyalinization of the loops. This may perhaps be correlated with the lower blood pressure in the cases of this group. As regards etiology, it may be noted that Case 5 of the former group and Cases 12 and 15 of this group originated apparently in pregnancy.

We conclude, therefore, that these four cases which we have grouped together do not constitute a distinct type of nephritis either clinically or anatomically, but that, owing perhaps to a greater involvement of the tubular epithelium and perhaps to less pronounced cellular proliferation in the glomeruli, they exhibit a somewhat altered picture with a tendency to more edema of the so-called renal type, more albuminuria, a greater abundance and variety of casts, a higher concentration of the plasma chlorids and less increase in the blood urea, less reduction in the phenolsulphonephthalein, less fixation of the urinary specific gravity and less elevation of the blood pressure.

We wish to emphasize at this point, however, that the distinctions just named ought not, we believe, be taken as evidence that the excretion of urea and phenolsulphonephthalein is a function of the glomeruli. The factors are much too complex to warrant such conclusions from cases that resemble each other so closely as do those of these two groups. Moreover, there is good experimental evidence to support the view that the chief excretion of both urea and phenolsulphonephthalein is a function of the tubules. This view is supported by the fact that, in the early stages of glomerulonephritis, when the anatomic lesions are in many cases practically confined to the glomeruli, although the blood pressure is elevated, the blood urea and the phenolsulphonephthalein excretions are quite normal. Later, in the advanced stages, when the blood urea and the phenolsulphonephthalein are markedly

altered, there is always extensive obliteration of a large number of the renal tubules secondary to the fibrosis and obliteration of their associated glomeruli.

We are disposed to apply to such cases as those in the group that includes Cases 12 to 15 the simple term chronic nephritis or chronic diffuse nephritis without further qualification, and to reserve for the typical cases of the former group the more specific term chronic glomerulonephritis.

Arteriosclerosis.—The series includes nine cases of arteriosclerosis with cardiac decompensation (Cases 16 to 24); four with necropsy. The kidneys of these cases varied to a considerable degree. Two were grossly of the so-called arteriosclerotic type; one was a small, pale kidney; one was normal grossly. Histologically, they showed practically normal glomeruli; little or no change in the tubular epithelium; little interstitial fibrosis; more or less marked sclerosis of the larger arteries and less or none of the smaller vessels; and a more or less marked degree of passive congestion which in Case 18 was very intense. The blood pressure in these cases was for the most part a little lower than those seen in the cases of chronic glomerulonephritis, and the ratio of pulse pressure to systolic pressure was lower in this group. A fall of blood pressure occurred as death approached, but, as noted in the former group, the fall in pulse pressure was, to our surprise, not greater relatively than is the fall in systolic pressure. The phenolsulphonephthalein excretion was moderately good, being over 20 per cent. in two hours in all but two cases which were studied about a month before death when cardiac decompensation was quite marked. In one case an elimination of 60 per cent. was observed. Increase in blood urea or nonprotein nitrogen was of very moderate proportions. The plasma chlorids were normal or approximately normal in the cases studied. The plasma bicarbonates were but little lowered except in one case. Urinary specific gravity exhibited about the same range as would be seen in a similar series of normal cases and showed little tendency to fixation.

Three additional cases (25 to 27) were also instances of arteriosclerosis, but the presence of edema of the face, headache, vomiting and impaired vision suggested the association, in addition, of more or less chronic nephritis. Two of these cases coming to necropsy confirmed this suspicion, since both exhibited, in addition to arteriosclerosis, a rather early stage of chronic glomerulonephritis with cellular proliferation in the tufts. The blood pressure and the relative pulse pressure in these cases was higher than in arteriosclerotics and resembled that of the chronic glomerulonephritis group. The phenolsulphonephthalein was moderately reduced. The blood urea or non-

protein nitrogen exhibited an increase intermediate between the slight increase of the arteriosclerotics and the marked increase of the late glomerulonephritics. Plasma chlorids, plasma bicarbonate and urinary specific gravity correspond rather with the observations in the arteriosclerotic group. (These cases are presumably instances of what Volhard and Fahr[8] in their recent monograph have called "Kombinationform.") In Case 26 the history is inadequate. In the other two cases recent infections, pneumonia and acute rheumatism, had occurred and may be considered as probable causes of the nephritis superimposed on the arteriosclerosis.

Miscellaneous.—Cases 28 and 29 exhibited what we interpret as a somewhat confusing combination of weakened myocardium and chronic diffuse nephritis. In the tendency to slight elevation of blood pressure and to edema of face these cases suggest chronic nephritis. The renal functional tests, however, indicate strikingly little impairment of renal function.

Case 30 exhibits a rather pronounced impairment in certain of the renal functional tests, but at necropsy showed merely a pronounced fatty degeneration of the epithelium of the convoluted tubules. It illustrates how marked an impairment of phenolsulphonephthalein excretion and accumulation of waste nitrogen in the blood can result from a purely tubular lesion or occur with no other renal lesion than this.

CONCLUSIONS

1. The cases of acute nephritis showed rather a pronounced impairment of all the renal functional tests.

2. The cases of advanced chronic glomerulonephritis showed, in the most pronounced degree, elevation of blood pressure, depression of phenolsulphonephthalein excretion, elevation of blood urea or nonprotein blood nitrogen, fixation of urinary specific gravity and the presence of albuminuric retinitis.

These cases were characterized, however, by a normal or even a definitely subnormal plasma chlorid level, and by a considerable reduction of the plasma bicarbonates.

Those cases which exhibited marked tendency to proliferative changes in the glomerular tufts were characterized, as a rule, by higher blood pressure than the cases which exhibited chiefly hyaline changes in the tufts.

3. The cases which might have been classed clinically as chronic parenchymatous nephritis or as nephroses, because of the very slight elevation of blood pressure, the less marked depression of phenolsulphonephthalein, the less marked elevation of nonprotein nitrogen and

8. Volhard, F., and Fahr, Th.: Die Brightsche Nierenkrankheit. Berlin, 1914.

TABLE 1.—

Case		Clinical Diagnosis	Sex	Age	Symptoms of Onset	Anemia	Blood Pressure
1	L. H.	Acute septic nephritis; septicemia	♀	36	Sepsis following abortion...	Moderate	157- 91 86- 59
2	C. J.	Acute postinfectious glomerulonephritis	♂	35	Edema face and feet; oliguria; anorexia	None	155–105 130- 80
3	J. J. McF.	Early chronic nephritis.....	♂	24	Edema face, hands and feet; headache; lumbar pain	Slight	145- 90 135- 80
4	G. P.	Advanced glomerulonephritis	♂	49	Headache; lumbar pain; edema of face	Moderate	210–145
5	F. G.	Advanced glomerulonephritis (pregnancy)	♀	35	Headache; vomiting; dyspnea, edema of feet, impaired vision	Moderate	230–170 140- 90
6	W. M.	Advanced glomerulonephritis. Terminal infection (?)	♀	38	Oliguria, loss of consciousness, convulsions	Slight	160–100 135- 90
7	M. W.	Chronic glomerulonephritis	♀	28	Weakness; vomiting; headache; vertigo; abdominal pain	Marked	260–175 190–120
8	A. C.	Areteriosclerosis; chronic glomerulonephritis	♀	61	Headache.....	Slight	260–135 190–120
9	J. W. C.	Chronic glomerulonephritis	♂	46	Weakness; tires easily.....	Moderate	160- 95 140- 85
10	F. K.	Advanced glomerulonephritis	♂	34	Headache; vomiting; abdominal pain	Slight	178–115 120- 85
11	W. L.	Advanced glomerulonephritis	♂	28	Lumbar pain; vomiting; headache	Moderate	215–130 150- 90
12	E. M.	Chronic nephritis (pregnancy)	♀	42	Lumbar pain; impaired vision; headache; edema face and feet; eclampsia	None	210–130 200–125
13	R. C.	Chronic nephritis	♀	15	Edema face and feet; headache; impaired vision; vomiting	Moderate	140- 95 125- 85
14	M. O.	Chronic nephritis	♀	24	Abdominal pain; vomiting; weakness	Moderate	170- 80 145- 75
15	S. G.	Chronic nephritis (pregnancy)	♀	20	Edema face; headache impaired vision; vertigo	Marked	165–105 128- 85
16	J. F.	Arteriosclerosis; cardiac decompensation	♂	57	Weakness: dyspnea.....	None	180–130 165–110
17	H. R.	Arteriosclerosis; cardiac decompensation	♂	69	Edema face and legs; dyspnea; oliguria	Slight	105- 75 98- 75
18	F. S.	Arteriosclerosis; cardiac decompensation	♂	68	Edema legs; dyspnea; weakness	Slight	150- 95 130- 90
19	D. E.	Arteriosclerosis; cerebral hemorrhage	♂	54	Apoplexy.....	Slight	220–160 145- 95
20	C. S.	Arteriosclerosis; cardiac decompensation; luetic	♂	38	Dyspnea; weakness; cough; edema legs	None	195–125 170–110
21	R. W.	Arteriosclerosis; cardiac decompensation; luetic	♂	40	Edema of legs; dyspnea; oliguria	Slight	195–100 135- 75
22	H. J. B.	Arteriosclerosis; cardiac decompensation; emphysema	♂	54	Edema legs; dyspnea.....	None	175–110
23	M. M.	Arteriosclerosis; cardiac decompensation	♀	57	Cough; dyspnea; edema back, legs and face	None	145–100 100- 70
24	P. H.	Gastric carcinoma; cardiac decompensation	♂	54	Epigastric pain; dyspnea; weakness; edema legs	Severe	123- 65
25	S. P.	Arteriosclerosis; chronic nephritis; cardiac decompensation	♂	50	Edema legs; dyspnea; vomiting; headache	Moderate	240–130 205–110
26	J. M. B.	Arteriosclerosis; chronic nephritis; cerebral hemorrhage	♂	45	Headache; apoplexy.....	Slight	260–135 190–120
27	G. M.	Arteriosclerosis; chronic nephritis	♀	50	Cramps in legs; weakness; edema of feet and face; headache; impaired vision	None	265–160 160- 90
28	W. W. B.	Postinfectious myocarditis; early chronic nephritis	♂	36	Dyspnea; cough; edema face	Slight	140- 87 180–125
29	F. F.	Chronic nephritis; cardiac decompensation	♂	35	Edema feet and face; dyspnea; vomiting; oliguria	Slight	145–105 160- 85 135- 65
30	L. C.	Heroin habitué; asthenia; gastroenteritis	♂	20	Diarrhea; vomiting; weakness	None	105- 80 95- 60

Phenol-sulphone-phthalein	Blood Urea N.	Non-protein Blood N.	Plasma NaCl	Plasma CO_2	Urinary Specific Gravity	Eyegrounds	Termination
0	.....	112–227	.....	.....	1.008–1.014	.....	Pulmonary edema; death
41–60	52–10	.....	6.5–5.9	61–60	1.015–1.018	.....	Improved
50	12	.....	5.5	71	1.015–1.018	.....	Improved
0	102	.....	5.7	49	1.010–1.012	Sclerosis; hemorrhage	Unimproved
0	125–148	.....	6.1–4.9	36–53	1.010–1.012	Albuminuric retinitis	Unimproved
.....	185	.....	4.6	48	.....	.....	Convulsions; pulmonary edema; death
45–50	.....	.....	.....	.....	1.015–1.033 1.009–1.013	Albuminuric retinitis	Coma; pneumonia; death
10	.....	.....	.....	.....	1.005–1.010	Albuminuric retinitis	Coma; death
2	.....	127	.....	.....	1.012	Normal	Coma; death
Trace	195	.....	5.5–5.6	36	1.009–1.011	.....	Coma; death
9	.....	108–200	.....	.....	1.011–1.013	Albuminuric retinitis	Pericarditis; death (cardiac)
.....	29	.....	6	.....	1.013–1.015	.....	Improved
33–50	17–23	.....	6.6–6.2	60	1.010–1.017	Fullness of veins	Cardiac failure; death
22–0	.....	78	.....	.....	1.012–1.021 1.010–1.012	.....	Coma; death
22–5	.....	81	.....	.....	1.009–1.020	.....	Oliguria; death (cardiac following decapsulation)
15	.....	.....	.....	.....	1.020–1.021	.....	Cardiac; death
.....	.....	30	.....	.....	1.018–1.025	.....	Pneumonia; death
13	.....	48	.....	.....	1.020–1.025	.....	Cardiac; jaundiced; death
30	.....	35	.....	.....	1.021	.....	Apoplexy; pulmonary edema; death
35	17	.....	5.6	.....	1.017–1.021	.....	Improved
20	35–17	.....	5.9–5.8	46–53	1.021–1.025 1.007–1.012	.....	Improved
27–35	23–9	.....	5.7–5.5	56–61	1.008–1.012	.....	Improved
60	20	.....	5.9	57	1.005–1.010	.....	Improved
48	29	.....	6.0	66	1.012–1.017	.....	Unimproved
30–16	26–52	.....	5.8–6.3	63–52	1.012–1.022	Albuminuric retinitis	Improved
.....	58	.....	5.5	61	1.007	.....	Apoplexy; death
21–12	.....	72	.....	.....	1.009–1.020	.....	Coma; Cheyne-Stokes; circulatory death
42–32	15–20	.....	5.9–5.5	59–65	1.013–1.027	Normal	Improved
50–60	12–19	.....	6.0–5.7	35–53	1.017–1.021	Normal	Improved
7	.....	55	.....	.....	1.003	.....	Collapse; death

the more nearly normal urinary specific gravity, and because they exhibited conspicuous edema, especially of the face, and abundant albumin and casts of all kinds in the urine — these cases were less definitely characterized histologically than had been expected. While it is true that they showed pronounced degenerative or necrotic changes in the tubular epithelium, they also showed conspicuous, even advanced glomerulonephritis. Histologically, their separation from the clinical group of advanced glomerulonephritis would have been difficult, perhaps impossible. Grossly, the kidneys in these cases were identical with those of the other group just mentioned. We prefer to call these cases simply "chronic nephritis" without further qualification.

The plasma chlorids were elevated in the two cases of this group studied in this connection.

4. The cases which clinically and histologically were cases of renal arteriosclerosis, exhibited a variety of forms of kidney, grossly, and could not have been properly classified on gross appearance alone. The blood pressure, and especially the pulse pressure, although much above normal, were usually lower than in cases of advanced glomerulonephritis.

The plasma chlorids and plasma bicarbonates were normal or approximately so.

5. In all cases with elevation of blood pressure some fall of pressure was noted in the last five or ten days before death. Contrary to expectation, however, the fall in diastolic pressure was closely proportional to the fall in systolic pressure, and not less, as would have been expected.

PROTOCOLS OF CASES

CASE 1.—*Acute Diffuse and Suppurative Nephritis Following a Septic Endometritis with Pyemia.*

L. H., woman, aged 26, was admitted three weeks before death because of abdominal pain.

The patient had had measles in childhood; scarlet fever at 26. For several years she had had attacks of otitis media. Two months before death, following a severe nervous shock, she developed a recurrence of otitis media. A month before death an abortion was attempted, followed by abdominal pain, diarrhea, a slight fever and a leukocytosis of 18,000. The leukocytosis increased to 55,000, with 88 per cent. of polymorphonuclear neutrophils a week before death, and then declined to 28,000 with the same differential percentile count. The patient grew progressively weaker, developed acute suppurative parotitis, followed by cellulitis, a progressing anemia and died with pulmonary edema.

The phenolsulphonephthalein test showed no excretion during the last two weeks. The total nonprotein nitrogen was as follows: 16 days before death, 112 mg. per cubic centimeter; 14, days, 144 mg.; 12 days, 179 mg.; 9 days, 227 mg.; 7 days, 208 mg.; 5 days, 112 mg. The fall in blood nitrogen during the last week was associated with the development of persistent vomiting. The blood pressure was 118-82 twenty-one days before death and rose to 157-91 fourteen days before death. The urine was of good volume to the end; specific

gravity, from 1.008 to 1.014; albumin, from a light cloud to solid; casts regularly absent; pus abundant; erythrocytes usually in considerable numbers.

At necropsy there was found septic endometritis; cellulitis and suppurative otitis of the entire right ear; multiple small abscesses in the lungs. The kidneys were large, red and flabby. Histologically most of the glomeruli exhibited some degree of acute intracapillary glomerulonephritis; in many this was scarcely noticeable, in others it was quite marked and there was desquamation and exudation in Bowman's capsule. The tubules exhibited granular degeneration and some contained desquamated epithelium and many erythrocytes. There was marked interstitial hyperemia and edema and areas of lymphocytic and polymorphonuclear infiltration that constituted minute abscesses.

CASE 2.—*Acute Glomerulonephritis with Tubular Involvement; Recovery.*

C. J., man, aged 35, colored, admitted Sept. 26, 1916, because of edema of the feet, legs and scrotum; discharged Nov. 27, 1916, improved.

The patient had measles in childhood; gonorrhea at 19; used alcohol freely. Three weeks before admission he developed feverishness and pains in the extremities. Two weeks later he noticed swelling of the feet and face and later of the legs and scrotum; the urine was scanty and reddish; there was loss of appetite.

On admission he presented edema as described; slight icterus seen in the sclerae; the heart of normal size; first sound of poor tone; second, slightly accentuated; the urine, 400 to 1,000 c.c. on admission, rose to 2,000 c.c. before discharge; the specific gravity was from 1.015 to 1.018; albumin, at first, almost solid, later reduced to traces; at first, abundant hyaline, granular and leukocytic casts, a few erythrocytes, many leukocytes and renal epithelium; on discharge no casts, leukocytes and epithelium about normal, still a few erythrocytes. The blood pressure fell from 155-105 to 130-80. The blood count was normal; the Wassermann, negative.

	Phenolsulphonephthalein	Blood Urea N.	Plasma Chlorids	Plasma CO_2
Admission	41	52	6.5	61
Discharge	60	10	5.9	60

The patient was kept on a salt-free, low protein diet, with limited fluid intake. He was discharged free of edema, having lost 40 pounds.

CASE 3.—*Early Chronic Glomerulonephritis.*

J. J. McF., man, aged 24; was admitted Dec. 28, 1916, because of weakness, headache, and lumbar pain.

The patient had had typhoid at 12, pneumonia at 14, was subject to colds and sore throat and had a chronic cold. A year before admission he had a sudden attack of edema of the face; later of legs and hands. He was admitted to a hospital with blood pressure of 220 and kept in the hospital four months. His urine had since continued to show evidences of nephritis. Eight weeks before admission here, following a chilling, he developed headache, chills and lumbar pains. These persisted or increased until admission. He had formerly been a heavy drinker; teeth very poor, with much pyorrhea. Enlarged post cervical glands; heart slightly enlarged, sounds normal. The urine was 100 to 200 c.c. in amount; specific gravity from 1.015 to 1.018; albumin, from a cloud to a trace; casts, hyaline and granular, sometimes many, sometimes very few. The blood pressure ranged from 145-90 to 135-80. The blood showed a slight anemia; Wassermann negative.

CASE 4.—*Advanced Glomerulonephritis.*

G. P., man, aged 49; was admitted Oct. 11, 1916, for headache and lumbar pain.

The patient had had no previous illnesses; had always been a heavy eater of meat; had taken four or five glasses of beer daily; a heavy tea drinker and

moderate user of tobacco. The symptoms began about seven months before admission as attacks of severe pain in the back of the neck, followed by headache and vertigo; frequently dull lumbar pain; slight puffiness about the eyes.

On admission the patient was pallid; had enlarged posterior cervical lymph nodes; heart slightly enlarged; slight aortic systolic murmur; greatly accentuated second aortic sound. The urine was normal in amount; specific gravity from 1.010 to 1.012; albumin, a cloud; occasional granular casts; increased leukocytes. The blood pressure was 210-145. The blood count showed a moderate anemia. The eyegrounds showed sclerotic vessels, a small hemorrhage, areas of fatty degeneration, but not typical albuminuric retinitis.

CASE 5.—*Advanced Glomerulonephritis.*

J. G., woman, aged 35; was admitted Nov. 14, 1916, for dyspnea; discharged Dec. 27, 1916, not improved.

The patient had had measles, mumps and whooping cough in childhood. Four years before admission she was delivered of a 7 months' dead child following a threatened eclampsia with impaired vision; thereafter, subject to severe headaches, sometimes with vomiting. She had a light case of scarlet fever two years before admission. Two months before admission she noticed dyspnea worse at night; progressive impairment of vision and slight edema of the feet.

On admission the heart was enlarged; systolic mitral murmur; accentuated second sound; slightly enlarged liver; little or no edma. The urine was normal in amount; specific gravity from 1.010 to 1.012; albumin, a heavy cloud; no casts; a slight increase of leukocytes. The blood pressure ranged from 230-170 to 140-90. The blood showed a moderate anemia; the Wassermann was negative. The eyegrounds showed sclerosis, hemorrhages, exudates and blurring of the margins of the disks. She was kept on a low protein, salt-free diet with 3 gm. each of sodium citrate and sodium bicarbonate per day.

Date	Phenolsulphonephthalein	Blood Urea N.	Plasma Chlorids	Plasma CO_2
11/15	0	125	6.1	36
11/24	—	145	5.5	44
12/ 1	—	148	5.4	53
12/20	—	127	4.9	53

Dec. 20, 1917, she had two convulsions, following which 20 ounces of blood were removed, the functional study of which date was made twelve hours later.

CASE 6.—*Advanced Glomerulonephritis. Terminal Infection (?).*

W. M., woman, aged 38; was admitted six days before death for unconsciousness and convulsions.

The patient had had smallpox at 6; for twenty years she had had lumbar pain, worse the last six years; had been a free drinker of beer. Two years previously she had had diphtheria. Five months prior to admission she had had a supravaginal hysterectomy for carcinoma of the fundus, followed by radium treatments. For a few days before admission the patient had noticed progressive oliguria. During the twelve hours before admission she was unconscious, with three convulsions. The heart was slightly enlarged; a mitral systolic murmur was present. There was almost complete anuria; 10 c.c. of urine obtained by catheter was bloody and contained a light cloud of albumin, no casts, many erythrocytes, and was loaded with leukocytes. The blood pressure ranged from 160-100 to 135-90. The blood showed a slight anemia; a leukocytosis of 23,000 with 91 per cent. polymorphonuclear neutrophils; Wassermann negative. Lumbar puncture gave normal fluid. She had a temperature of 104 F. a few hours before admission, falling then below normal, to rise in the last twelve hours to 102. She had repeated convulsions until death ensued, with pulmonary edema. Necropsy was refused.

	Blood Urea N.	Plasma Chlorids	Plasma CO_2
Five days before death.....	185	4.6	48

This study was made twelve hours after a venesection of 300 c.c., with introduction of 240 c.c. of physiologic sodium chlorid solution.

CASE 7.—*Chronic Glomerulonephritis.*

M. W., woman, aged 28; colored; admitted two months before death complaining of vomiting, pain in the stomach and headache.

The patient had had measles as a child, frequent attacks of indigestion, with distention. Four years before she had had rheumatic fever. For three years she had had pain and tenderness in the left hypochondrium, worse after eating; later, vomiting became associated with these attacks. Severe headaches were frequent and associated with vertigo and weakness.

On admission the tonsils were found to be enlarged; the heart enlarged to both right and left, especially the latter, with accentuated second aortic sound. The urine was normal in amount. During the first two weeks the specific gravity ranged from 1.005 to 1.033; subsequently it remained from 1.009 to 1.013. Albumin was present in traces or moderate clouds. Casts were sometimes absent; sometimes occasional hyaline or granular casts were seen. Five weeks before death she had an attack of severe left-sided abdominal pain, with nausea; the left kidney became palpable and cystoscopic examination revealed only a little bloody urine coming from the left ureter. The blood pressure ranged from 260-175 to 200-125 until three days before her death, when it fell to 190-120. The phenolsulphonephthalein excretion sixty days before death was 45 per cent. for two hours; forty-six days before death, 10 per cent.; twenty-one days before death, 10 per cent.; sixteen days before death, 5 per cent. Forty days before death there was no elimination of indigocarmin in thirty minutes. The eyegrounds two months before death showed extensive arteriosclerosis of the retinal vessels, with numerous exudates about the posterior pole. Two weeks later the eyegrounds showed fresh exudates. The blood count, normal two months before death, fell to 30 per cent. of hemoglobin and 2,200,000 red blood cells two weeks before death. During the last week the patient was stuporous and vomited persistently. The lobar pneumonia found at necropsy was unrecognized during life and gave no rise of temperature and no notable increase in the already pronounced dyspnea. For the last month considerable edema of the legs was present and also hydrothorax, hydropericardium and ascites. The Wassermann was negative.

At necropsy there was found lobar pneumonia of the right lower lobe; hydrothorax, hydropericardium, ascites, a healed tuberculous lesion at the left apex; caseous bronchial lymph nodes; cloudy swelling and fatty degeneration of the liver. The kidneys were about normal in size, pale, with cysts. In the lower pole of the left kidney was a large hemorrhagic infarct showing at its edges beginning organization; this was doubtless the cause of the pain and hematuria five weeks before death.

Histologically an occasional glomerulus was fibrous and obliterated, but almost all showed little change; there was slight cellular proliferation in the tufts. The tubules were for the most part somewhat dilated, with flattening of the epithelium and some granular degeneration. There was rather marked diffuse increase of the interstitial fibrous tissue throughout the cortex, and, to a much less marked degree, in the medulla. The smaller vessels showed thickened walls. Throughout there was moderate congestion.

CASE 8.—*Arteriosclerosis and Chronic Glomerulonephritis.*

A. C., woman, aged 61; was admitted fifteen days before death because of headache.

There was a previous history of discharging ears for some years and frequent attacks of severe headache. Six weeks before death the patient became suddenly unconscious; recovered in a few days but remained confused, weak, with severe headache, defective vision, palpitation and polyuria.

On admission there was slight edema of the ankles, the heart was enlarged both to the right and left, with mitral and aortic systolic murmurs. The urine was abundant; specific gravity from 1.005 to 1.010; albumin, a cloud; casts varying from none to many granular. The blood pressure ranged from 240-150 to 150-100 shortly before death. The phenolsulphonephthalein excretion twelve days before death was 10 per cent. for two hours. Both eyegrounds showed an albuminuric retinitis with exudates, hemorrhages and sclerosis. Death occurred in coma.

The kidneys histologically showed almost half their glomeruli obliterated by fibrosis; the remainder exhibited marked cellular proliferation and round cell infiltration; the remaining tubules showed slight granular degeneration and the lumina contained a little precipitated albumin. There was marked fibrosis of the medulla. The vessels had greatly thickened, sclerotic walls.

CASE 9.—*Chronic Glomerulonephritis.*

J. W. C., man, aged 46; a typesetter, exposed to lead; admitted eighteen days before death for weakness and a tendency to tire quickly.

No infections in childhood were recalled. He began work as a typesetter at 16. Since the age of 21 he had been subject to occasional epileptiform attacks; more frequent recently. At 39 he had an attack of acute articular rheumatism lasting three months; had slight indigestion for several years. A month before death he noticed that he tired easily and his legs felt heavy.

On admission he was observed to be a pallid, slightly sclerotic individual; heart moderately enlarged, with mitral and aortic systolic murmurs; the liver a trifle enlarged. The urine was normal in volume; specific gravity persistently 1.012; albumin, a moderate cloud; abundant hyaline, granular and epithelial casts. The blood pressure ranged from 160-95 to 140-85. The eyegrounds were normal. The Wassermann was negative. The blood showed hemoglobin 40 per cent.; red blood cells, 3,000,000; no signs of basic degeneration. No lead line was present, nor was there any neuritis. A terminal pericarditis and pleuritis developed and he succumbed, with pulmonary edema.

Only partial necropsy was permitted. The kidneys were pale, granular and contracted. Histologically the glomeruli exhibited all stages of destruction by fibrosis and hyalinization of the tufts. A few were completely obliterated. All showed destruction of one or more capillary loops. The capsules were thickened. All of the tubules were more or less encroached on by interstitial hyperplasia. The tubular epithelium exhibited flattening and atrophy and a moderate granular degeneration and the lumina of many were dilated and contained albumin and casts. In one area the capsular spaces of four glomeruli and the lumina of the associated tubules were filled with blood. The medulla showed extensive fibrosis, with distortion of the tubules. Vascular sclerosis was slight.

CASE 10.—*Advanced Chronic Glomerulonephritis.*

F. K., man, aged 34; a paper hanger; admitted three weeks before death for weakness and vomiting.

The patient had had the more trivial infections of childhood; repeated attacks of quinsy; had had a chronic suppurative otitis media for twenty-five years; gonorrhea at 19. A year before death the patient began to have attacks of headache, with vomiting, at times with abdominal pain and cramps in his legs. Seven weeks before death he began to suffer with dyspnea, cough and a sense of smothering.

On admission he was pallid; moderately sclerotic; teeth in very bad condition; heart enlarged both right and left, with a mitral regurgitant murmur and accentuated second sounds. The Wassermann was negative. There was a slight anemia. The urine was of normal volume; specific gravity from 1.009 to 1.011; albumin from a trace to a moderate cloud; casts, sometimes many hyaline and granular, sometimes none. The blood pressure, 178-115, fell before death to 120-85. The phenolsulphonephthalein, two weeks before death, was only a trace. The blood urea nitrogen, ten days before death, was 195 mg.

per 100 c.c.; the plasma chlorids from 5.5 to 5.6 gm. per liter; the plasma bicarbonate, 36 volumes per cent.

Only partial necropsy was permitted. The kidneys were small, granular and contracted. Histologically about half to two thirds of the glomeruli were wholly fibrous and obliterated and these appeared to be grouped in certain areas. Here the tubules were collapsed, atrophic and almost obliterated by the interstitial hyperplasia and round cell infiltration. In other areas the glomeruli showed no fibrous hyalinization or thickening of the capsules, but did exhibit a cellular proliferation in the tufts. In these areas the tubules were more nearly normal and showed only a slight granular degeneration of the epithelium, with albumin and casts in the lumina. The medulla showed a rather cellular interstitial hyperplasia of moderate grade. The vessels exhibited a marked sclerosis. The glomerulonephritis was apparently very advanced in certain areas, while in intermediate zones it appeared to be comparatively early.

CASE 11.—*Advanced Chronic Glomerulonephritis.*

W. L., man, aged 28; was admitted five weeks before death because of vomiting, headache and impaired vision.

The patient had had chickenpox in childhood; five years before death he had had gonorrhea; about the same time he had had sudden attacks of lumbar pain and was told at that time that he had Bright's disease. Two months before admission he began to have attacks of vomiting associated with severe frontal headache. A month later his vision became seriously impaired.

On admission he was pallid; had a slight adenopathy; beaded, sclerotic arteries; tonsils enlarged and the right tonsil ulcerated and infected with the characteristic organisms of Vincent's angina; the heart was enlarged to the right and left, with short, inconspicuous systolic and diastolic murmurs at both apex and base. The urine varied in amount from 800 to 2,000 c.c.; the specific gravity fixed from 1.011 to 1.013; albumin, about 2.5 gm. per liter (Esbach); many hyaline, light and dark granular casts; leukocytes somewhat in excess of normal; a few doubly refractile lipoids. The blood pressure ranged from 215-130 on admission to 150-90 the day before his death. The phenolsulphonephthalein excretion on admission was 9 per cent. for two hours. The total nonprotein blood nitrogen was from 118 to 108 mg. per 100 c.c. soon after admission, and 200 mg. three weeks before death. The eyegrounds on admission showed a neuroretinitis, with marked exudates and flame-shaped hemorrhages. The blood count was persistently about 60 per cent. of hemoglobin; red blood cells, 2,700,000. The Wassermann was negative. Three weeks before death dyspnea became intense and edema of the legs and enlargement of the liver developed. A week before death a pericardial friction appeared. He succumbed from circulatory weakness.

At necropsy the heart was hypertrophied; the aortic valves sclerotic; bilateral hydrothorax; passive congestion of all the viscera, with some fibrosis. The kidneys were small, pale, capsule adherent, surface finely granular and studded with several small cysts. Histologically three fourths of the glomeruli were wholly fibrous and obliterated; the remainder showed marked cellular proliferation in the tufts and some thickening of the capsules. The tubules around the obliterated glomeruli were collapsed, with atrophied epithelium, and were almost obliterated by the marked cellular interstitial hyperplasia and round cell infiltration. The tubules near the intact glomeruli were somewhat distended and showed a moderate granular degeneration and some flattening of their epithelium; their lumina contained precipitated albumin. The medulla showed a marked cellular interstitial proliferation and considerable congestion. There was marked thickening of the vessel walls.

CASE 12.—*Chronic Diffuse Nephritis.*

E. M., woman, aged 42, was admitted Nov. 1, 1916, for backache, impaired vision, edema of the face and legs; discharged Nov. 13, 1916, improved.

The patient had had measles and diphtheria in childhood; pneumonia at 35. During her third pregnancy, March to December, 1914, the patient suffered from pain in the lumbar region, and after delivery vision was impaired and she fatigued readily. During her fourth pregnancy, October, 1915, to June, 1916, she had albuminuria, edema of the feet and one convulsion; after delivery a second convulsion, edema of the feet and face and severe headaches; subject to colds and coughs.

On admission the heart was enlarged; second sound accentuated; slight edema of the legs. The urine was normal in amount; specific gravity from

TABLE 2.—

Case No.	Gross Appearance	Glomular Involvement	Tubular Degeneration	Tubular Dilatation	Fibrosis Cortex
1	Large red	Acute	Granular	None	Abscesses
7	Small white	Early chronic (proliferative)	Atrophy; granular	Moderate	Marked
8	.....	Intermediate chronic (proliferative?)	Granular	None	None
9	Small white	Intermediate chronic (hyaline?)	Atrophic; granular	Moderate	Marked
10	Small	Advanced chronic (proliferative)	Slight granular	None	Only around obliterated glomerull
11	Small white	Advanced chronic (proliferative)	Granular	Moderate	Slight except around obliterated glomerull
14	Small	Intermediate chronic (Mixed)	Granular fatty	None	Marked
15	Small	Advanced chronic (hyaline)	Atrophic; marked desquamation	Moderate	Moderate
16	Normal	None	None	None	None
17	Arteriosclerotic	None	Slight granular	None	None
18	Arteriosclerotic	None	Granular	None	None
19	Small white	None	None	None	None
26	Small red	Early chronic (proliferative)	None	Moderate	Marked
27	Small red	Intermediate chronic (proliferative?)	Slight	Marked	None
30	Large white	None	Fatty	None	None

1.013 to 1.015; albumin, a cloud; a few hyaline casts; many leukocytes. The blood pressure ranged from 210-130 to 200-125. The blood count was normal; the Wassermann was negative.

CASE 13.—*Chronic Diffuse Nephritis.*

R. C., girl, aged 15, was admitted June 21, 1916, for anasarca; discharged Sept. 30, 1916, slightly improved.

The patient had had measles and whooping cough in childhood. Five months before admission she noticed edema of the feet associated with headache, black spots before the eyes, vomiting, all of gradual onset. There was general anasarca with involvement of the face; very pallid; tonsils enlarged and cervical lymph nodes palpable; heart normal in size; sounds, fair; no murmurs; bilateral hydrothorax and ascites. The urine ranged from 500 to 1,200 c.c. in amount; specific gravity, from 1.010 to 1.017; albumin, a heavy cloud; loaded with hyaline,

light and dark granular, epithelial and fatty casts; many leukocytes; abundant, doubly refractile lipoids, free, on casts and in compound granule cells and very large. The blood pressure ranged from 140-90 to 125-85. The phenolsulphonephthalein excretion varied from 33 to 50 per cent. in two hours after intravenous injection. The blood urea nitrogen was from 17 to 23 mg. per 100 c.c. The plasma chlorids 6.2 gm. per liter after two months on a salt-free low protein diet; the calculated threshold, 6.05 gm. The blood showed a moderate anemia and a persistent, slight leukocytosis of about 13,000 to 20,000. The eyegrounds show the disk anemic; kinking of the arteries and compression of the

—Pathological Data

Fibrosis Medulla	Arteriosclerosis		Congestion	Pathological Diagnosis
	Large	Small		
Cellular	None	None	None	Acute suppurative nephritis; acute glomerulonephritis
Moderate	None	Moderate	Moderate	Early chronic glomerulonephritis; arteriosclerosis
Marked	Marked	Marked	None	Arteriosclerosis; intermediate chronic glomerulonephritis
Marked	Slight	Slight	None	Intermediate chronic glomerulonephritis; arteriosclerosis
Cellular	Marked	Marked	None	Advanced chronic glomerulonephritis; arteriosclerosis
Cellular	Marked	Marked	Moderate	Advanced glomerulonephritis; arteriosclerosis
Marked	Marked	Marked	None	Arteriosclerosis; intermediate chronic glomerulonephritis; marked tubular involvement
Marked	Marked	None	None	Advanced chronic glomerulonephritis; marked tubular involvement; slight arteriosclerosis
Slight	Slight	None	Moderate	Arteriosclerosis; congestion
None	Slight	Slight	Marked	Arteriosclerosis; congestion
Slight	Moderate	Moderate	Intense	Arteriosclerosis; congestion
None	Marked	None	None	Arteriosclerosis
Marked	Marked	Marked	Marked	Arteriosclerosis; early chronic glomerulonephritis
Marked	Intense	Intense	None	Arteriosclerosis; intermediate chronic glomerulonephritis
None	None	None	None	Fatty degeneration

underlying veins, which were unduly full; pigmentation; doubtful evidence of old hemorrhages. The Wassermann was negative.

The patient died in another hospital Feb. 12, 1917, with cardiac symptoms, the death being from cardiac failure. Just before death the urine, blood and blood pressure were substantially those given. There was no necropsy.

Date	Phenolsulphonephthalein	Blood Urea N.	Plasma Chlorids	Plasma CO_2
7/ 5	50			
7/17	..	23	6.6	60
8/ 4	33			
9/ 1	..	17		
9/ 5	50			
9/16	..	20	6.2	

CASE 14.—*Chronic Diffuse Nephritis.*

M. O., woman, aged 24; admitted March, 1915, seventeen months before death, for pain in the lower abdomen, vomiting and weakness.

No previous illnesses. The patient had had occasional abdominal pain since a kick in her left side two years before admission. Vomiting and weakness developed just before admission. The urine was normal in amount; specific gravity from 1.012 to 1.021; albumin, a heavy cloud; casts, none at times, at others abundant hyaline and light granular casts. The blood pressure ranged from 170-80 to 145-75; the phenolsulphonephthalein from 12 to 20 per cent. for two hours; the total nonprotein blood nitrogen from 74 to 78 mg. per 100 c.c. The eyegrounds and blood count were normal. In November, 1915, in addition she developed edema of the face, headaches, vertigo and occasional diarrhea. The breath became urinous. The patient seemed somewhat stuporous. A moderate anemia was present. The urinary specific gravity was persistently 1.011 to 1.012; casts were always abundant. The blood pressure ranged from 155-95 to 118-60; the phenolsulphonephthalein excretion from 8 to 22 per cent. for two hours; the total nonprotein blood nitrogen was 67 mg. per 100 c.c. After a period of amelioration a return of symptoms with excessive vomiting and headache developed in July, 1916, a week before her death. The urinary output was diminished; the specific gravity from 1.010 to 1.012; albumin and casts as before. The blood pressure was 150-95; the phenolsulphonephthalein excretion, zero. Anemia was marked; hemoglobin, 45 per cent.; red blood cells, 2,750,000. The patient died comatose.

Only partial necropsy was permitted. The kidneys were small, granular, with adherent capsules. Histologically about one fourth of the glomeruli were completely obliterated; of the remainder all showed a little intracapillary proliferation and in some, hyalinization of one or more loops had taken place; the capsules were all more or less thickened. The tubules were greatly distorted by the marked cortical fibrosis and interstitial round cell infiltration. In many of the tubules the epithelium was flattened and atrophic. In the remaining tubules the epithelium showed marked fatty, granular degeneration. The medulla showed marked interstitial hyperplasia and the tubules for the most part contained casts. The vessels showed considerable sclerosis.

CASE 15.—*Chronic Diffuse Nephritis.*

S. G., woman, Jewess, aged 20; was first admitted 1913, eighteen months before her death, for swelling of the ankles and face, dyspnea, cough and vertigo.

She had had measles, diphtheria and pneumonia as a child. Beginning in 1909 she had had asthmatic attacks in damp weather. In January, 1912, at the age of 17, when five months pregnant with her only child, she noticed swelling of her ankles, black spots before her eyes and dizziness. Following a normal labor in May, 1912, these symptoms subsided, to return in a few months with, in addition, puffiness of the face and headaches.

When first seen, July, 1913, the urine showed a specific gravity of from 1.011 to 1.120; albumin 2 to 3.3 gm. per liter (Esbach); occasional hyaline and granular casts. The blood pressure was 165-105 on admission, falling after rest and treatment to 128-85. There was a slight anemia. The eyegrounds were normal. The phenolsulphonephthalein test gave an output of 22 per cent. in two hours and a month later of 15 per cent. In November, 1913, the heart was found somewhat enlarged to the left; paresthesias in the legs had developed. Hyaline and granular casts were abundant in the urine. The phenolsulphonephthalein excretion had fallen to 10 per cent. in two hours. The eyegrounds were still normal. Two months later she developed a bronchopneumonia which altered the picture but little except for a temporary depression of the blood pressure to 100-50 and a more marked anemia; hemoglobin, 57 per cent.; red blood corpuscles, 3,200,000.

In December, 1914, five weeks before her death, she was admitted again with symptoms unchanged. The blood pressure was 145-110. The urine showed albumin as before; the specific gravity ranged from 1.009 to 1.020; the urine was now loaded with hyaline and granular casts, contained many leukocytes

and many double refractile lipoids. The phenolsulphonephthalein elimination was 5 per cent. in two hours; the total nonprotein nitrogen, 81 mg. per 100 c.c. The anemia was progressing rapidly and three weeks before death the hemoglobin was 33 per cent.; the red blood corpuscles, 2,160,000. Vomiting now became frequent and the urinary output diminished. As a last resort decapsulation of the kidneys was performed, January 21. The patient died two days later. The Wassermann was negative.

Necropsy was refused, but it was permitted to remove the kidneys through the operative incision. They were small, pale reddish, with moderately adherent capsule, granular surface and numerous small cysts. Histologically the glomeruli were extensively diseased, being partially fibrous and extensively infiltrated with amyloid; the capsules were for the most part thickened; probably two thirds of the glomeruli were wholly obliterated. Many of the tubules, especially about the obliterated glomeruli, were collapsed, with atrophied epithelium and surrounded by hyperplastic connective tissue and round cell infiltration. The tubules about the glomeruli that were still partially intact showed extensive degeneration and often complete desquamation of the epithelium, and around the basement membranes of many was a moderate amount of amyloid infiltration. Most of these tubules contained casts. Throughout the cortex there was considerable interstitial fibrous tissue. A few of the tubules were distended with blood and others with leukocytes. The medulla exhibited a marked hyperplasia of the interstitial tissue, with compression of the tubules. The larger vessels showed a considerable degree of sclerosis.

CASE 16.—*Arteriosclerosis; Cardiac Decompensation.*

J. F., man, aged 57; was admitted three weeks before death for weakness, dyspnea and dryness of the mouth and throat.

This was a case of arteriosclerosis with cardiac decompensation. The urine amounted to from 300 to 1,200 c.c.; specific gravity, from 1.020 to 1.021; albumin, a trace to a cloud; many hyaline and granular casts. The blood pressure, 180-130, falling to 165-110 two days before death. The blood count was normal; the Wassermann negative. The phenolsulphonephthalein excretion on admission was 15 per cent. in two hours.

At necropsy the kidneys were of normal size and color, the capsule stripped easily, leaving a slight granular surface. Histologically the kidney was approximately normal. The medulla showed a moderate fibrosis. Throughout there was a moderate passive congestion. A few of the larger vessels showed thickened walls.

CASE 17.—*Arteriosclerosis; Cardiac Decompensation.*

H. R., man, aged 69, was admitted nine days before death because of edema and dyspnea.

The patient had had measles and scarlet fever in childhood; chancre in youth. Five years before death he developed discharging sinuses about his ankles, which remained open for two years. Eight months before death he began to show edema of the face in the morning, and later, of the legs and scrotum. Three days before admission he developed dyspnea, rapidly increasing edema and oliguria.

On admission the heart was enlarged; sounds feeble, with a mitral systolic murmur. A general anasarca was present. The urine was diminished in volume; specific gravity, from 1.018 to 1.025; albumin, a trace; at times a few hyaline and granular casts, at others, none. The blood pressure ranged from 105-75 to 98-75. The blood urea nitrogen was 30 mg. per 100 c.c.; the plasma chlorids, 5.9 gm. per liter; the plasma bicarbonates, 72 volumes per cent. The Wassermann was slightly positive. He developed a terminal pneumonia five days before death, with a slight transient rise of temperature to 101.3 F., and a leukocytosis of 18,000, of which 93 per cent. were polymorphonuclear neutrophils.

Only partial necropsy was permitted. The kidneys were of almost normal size (135 gm.); the capsule was slightly adherent; the surface was red and finely granular. Histologically there was pronounced congestion of the glomerular tufts and of the cervical and medullary vessels. Precipitated albumin was present in the capsular spaces and lumina of the tubules. Otherwise the glomeruli and tubules were approximately normal. The tubules exhibited a slight granular degeneration. The vessels were but little sclerosed and there was no hyperplasia of the interstitial tissue.

Case 18.—*Arteriosclerosis; Cardiac Decompensation.*

E. S., man, aged 68, was admitted five weeks before death for dyspnea and edema of the legs.

He had typhoid in boyhood, scarlet fever at 19 and his kidneys were said to have been affected for some time afterward. For three years before death he had moderate edema of the legs; later, with dyspnea and weakness. Six weeks before admission there was a brief attack of unconsciousness.

He was admitted with enlarged heart, poor cardiac sounds, congestion of the lungs and liver and anasarca. The urine was fair in quantity; specific gravity, from 1.020 to 1.025; albumin, a cloud; casts, at times abundant, hyaline and granular, at other times, none. The blood pressure was from 150-95 to 130-90. The phenolsulphonephthalein excretion on admission was 13 per cent. in two hours. At the same time the total nonprotein blood nitrogen was 48 mg. per 100 c.c. There was a slight anemia. The patient was jaundiced the last two days of his life. Death was from cardiac failure. At necropsy there was found marked arteriosclerosis involving especially the coronaries; cardiac hypertrophy and dilatation; recent infarcts in the lung and old infarcts in the kidneys. The kidneys were normal in size, hard, dark red; the capsule, slightly adherent; the surface, coarsely granular; one or two small cysts and old infarcts. Histologically there was throughout intense passive congestion. An occasional glomerulus was fibrosed but the great majority were normal except for the congestion. The tubules exhibited some granular degeneration of the epithelium and albuminous precipitate and sometimes a few erythrocytes in the lumina. The medulla showed little fibrosis. The vessels were moderately sclerotic.

Case 19.—*Arteriosclerosis; Cerebral Hemorrhage.*

D. E., man, aged 54; colored; admitted six days before death because of hemiplegia.

This was a case of cerebral hemorrhage occurring the day of admission in an arteriosclerotic with strongly positive Wassermann. The urine was of normal quantity; specific gravity, 1.021; a cloud of albumin; abundant hyaline, granular and epithelial casts. The blood pressure was 220-160 on admission, falling after venesection to 145-95. The total nonprotein blood nitrogen on admission was 35 mg. per 100 cc.; the phenolsulphonephthalein excretion two days later was 30 per cent. in two hours. At necropsy the kidneys were rather small and pale; the capsule stripped with difficulty, leaving a surface almost smooth. Histologically the kidney was almost normal. Occasionally a fibrosed glomerulus was seen, but the great majority were normal. A few showed a slight thickening of the capsule. The tubules were in good condition; in a few there was a little albuminous precipitate. Some of the larger vessels showed marked sclerotic thickening.

Case 20.—*Arteriosclerotic Hypertension with Cardiac Decompensation. Luetic.*

C. S., man, aged 38, was admitted Oct. 9, 1916, for dyspnea, weakness and cough; discharged Oct. 25, 1916, improved.

A case with strongly positive Wassermann; hypertension; very slight cardiac enlargement, chronic myocarditis and decompensation with slight enlargement of the liver and edema of the legs; blood count normal; the urine normal in amount; specific gravity, from 1.017 to 1.021; albumin, a faint trace; a moderate number of hyaline and granular casts; pus. The blood pressure was 170-110 to 195-125.

CASE 21.—*Arteriosclerosis; Cardiac Decompensation; Luetic.*

R. W., man, aged 40; was admitted Sept. 28, 1916, for edema of the trunk and legs, dyspnea and oliguria; discharged Nov. 5, 1916, improved.

The patient had measles, whooping cough and chickenpox in childhood; two attacks of appendicitis, unoperated; syphilis and gonorrhea at 28, the former treated for four years; used whisky to excess. Seven years before admission he began to have attacks of general stiffness, edema of the legs and oliguria; later he became dyspneic on exertion; these attacks had gradually increased in frequency and severity. On admission he exhibited intense edema of trunks and legs; pyorrhea alveolaris; congestion of the bases of the lungs; enlarged heart, initial systolic murmur and accentuated second pulmonic sound; palpable, tender liver. The urine was diminished in quantity; specific gravity, from 1.021 to 1.025; albumin, a cloud. Sometimes many hyaline, granular and occasionally epithelial casts; sometimes none. The blood pressure ranged from 135-75 to 195-100, the increase associated with clinical improvement. The blood count showed a slight anemia; the Wassermann was negative; eyegrounds were normal except for a slight indentation of the veins.

Date	Phenolsulphone-phthalein	Blood Urea N.	Plasma Chlorids	Plasma CO_2
9/29	20	35	5.9	46
11/ 2	..	17	5.8	53

The patient on a mixed, salt-free, low protein diet, with cardiac stimulation and fluid intake limited to 500 c.c. daily, did poorly. The oliguria persisted and the edema increased. About October 12 he developed diarrhea and mild jaundice. He was then placed on a milk diet (1,000 c.c. daily) and medication withdrawn. The diarrhea and jaundice promptly subsided; the urinary output rose to 3,600 c.c.; specific gravity, from 1.007 to 1.012, and the edema subsided with a loss of weight of 24 pounds in ten days. Shortly afterward the second functional studies were made.

CASE 22.—*Arteriosclerosis; Cardiac Decompensation; Emphysema.*

H. J. B., man, aged 54, was admitted March 23, 1917, for edema of the legs and dyspnea; discharged April 20, 1917, with compensation almost restored.

The urine was normal in amount; specific gravity, from 1.008 to 1.012; albumin, a cloud; casts abundant, hyaline, granular and a few leukocytic; later, after restoration of compensation, no casts. The blood pressure was about 175-110. The blood count was normal; Wassermann negative.

Date	Phenolsulphone-phthalein	Blood Urea N.	Plasma Chlorids	Plasma CO_2
3/26	27	23	...	60
4/ 2	29	23	5.7	56
4/20	35	9	5.5	61

The patient was kept on a low protein diet; fluid restricted to from 100 to 1,500 c.c.; strychnin, digitalis and sodium phosphate were given.

CASE 23.—*Arteriosclerosis; Cardiac Decompensation.*

M. M., woman, aged 57, was admitted Sept. 12, 1916, because of cough, dyspnea and edema of the back, legs and face; discharged Oct. 14, 1916, improved.

The patient had had measles and chickenpox in childhood, and was subject to occasional "sore throats." For a year she had had a troublesome cough; dyspnea on exertion; an increased edema of the legs, back and face. All the symptoms increased just before admission. On admission she presented, in addition, congestion of the pulmonary bases and enlarged heart, with initial systolic murmur and total arrhythmia (auricular fibrillation). The urine was normal in amount; specific gravity, from 1.005 to 1.010; albumin, a faint trace; no casts. The blood pressure ranged from 145-100 to 100-70. The phenolsulphonephthalein given intravenously was excreted to 60 per cent. in two hours (Sept. 17, 1916). The blood count was normal; the Wassermann negative; blood analyses were made Oct. 7, 1916.

The patient was discharged with edema and dyspnea diminished but not gone; auricular fibrillation persisting. She was kept on a salt-free, low protein diet, with limited fluid intake.

CASE 24.—*Carcinoma of the Stomach; Cardiac Decompensation.*

P. H., man, aged 54; was admitted Sept. 20, 1916, for pain in the epigastrium; discharged Oct. 10, 1916, unimproved.

This was a case of inoperable carcinoma of the stomach with little or no pyloric obstruction. There had been pain of four months' duration and dyspnea, weakness and edema of the legs for the same period; anemia was severe; Wassermann negative; urine normal in amount; specific gravity, from 1.012 to 1.017; albumin, a trace; many hyaline, granular and leukocytic casts. The blood pressure was 123-65. Eyegrounds normal, except for pallor.

CASE 25.—*Arteriosclerosis; Chronic Nephritis; Cardiac Decompensation.*

S. P., man, aged 50; was admitted June 19, 1916, for headache and edema of the feet; discharged July 17, 1916; readmitted Dec. 5, 1916; discharged March 16, 1917, improved.

The patient had had acute articular rheumatism at 15 and at 40. Since October, 1915, he had been more or less constantly in hospitals for edema of his legs, dyspnea and occasional attacks of vomiting. In April, 1916, he had pneumonia. On admission, considerable edema of the legs; heart slightly enlarged; vessels sclerotic. The urine was normal in amount; specific gravity, from 1.012 to 1.022; albumin, a heavy cloud; casts, sometimes none, sometimes many hyaline and granular. The blood pressure ranged from 240-130 to 205-110. The blood showed a slight to moderate anemia; Wassermann negative. The eyegrounds on June 20, 1916, showed sclerosis and hemorrhages, but no exudate or neuritis; on Dec. 8, 1916, in addition, the disk margins were hazy and a few exudates were seen.

Date	Phenolsulphonephthalein	Blood Urea N.	Plasma Chlorids	Plasma CO_2
6/21/16.....	30	26	5.8	63
12/ 6/16.....	18	52	6.3	52
2/12/17.....	16			

CASE 26.—*Arteriosclerosis; Chronic Nephritis; Cerebral Hemorrhage.*

J. M. B., man, aged 45; colored; admitted four days before death because of sudden loss of consciousness.

The patient had been subject to headaches and under treatment for Bright's disease for some time. He suddenly fell unconscious on the day of admission; exhibited a right-sided hemiplegia; Cheyne-Stokes respiration; heart enlarged to right and left; mitral systolic murmur; marked edema of legs. The urine was fair in quantity; specific gravity, 1.007; albumin, a heavy cloud; many hyaline, light and dark granular casts. The blood pressure ranged from 260-135 to 235-130 except after venesection, when it fell to 190-120. The blood urea nitrogen was 58 mg. per 100 c.c.; the plasma chlorids, 5.5 gm. per liter; the plasma bicarbonates, 61 volumes per cent. The blood showed a slight anemia; a leukocytosis of 15,000 with 86 per cent. polymorphonuclear neutrophils. The Wassermann was negative.

At necropsy there was left sided cerebral hemorrhage; a terminal, very recent pneumonia. The kidneys were small, red, and granular. Histologically there was marked congestion throughout. None of the glomeruli were obliterated but most showed moderate cellular proliferation in the tufts and a few, hyalinization of some of the loops; in a few there was a slight thickening of the capsule. The tubules appeared somewhat dilated, with fairly preserved epithelium; in the lumina of many were found albuminous precipitate and casts. The interstitial tissue in both cortex and medulla was considerably increased. The vessel walls were thickened.

CASE 27.—*Arteriosclerosis; Chronic Nephritis.*

G. M., woman, aged 50; was first admitted two years before death for general weakness, pains in the legs, edema of the feet and headache.

The patient had had measles, pertussis and chickenpox in childhood; malaria for three years at 20; at 25, an acute arthritis of the right knee and transient disturbance of vision; two years later, appendicitis, operated on; pneumonia at 41 and 44. Soon after this she was injured in a trolley accident; three ribs were broken and repeated small hemorrhages from the bowels occurred. For a year before admission she had cramplike pains in the legs and general weakness; slight edema of the feet and puffiness of the face in the morning; morning headaches; dyspnea on exertion; spots before the eyes and diplopia. The urine was of normal quantity; specific gravity, from 1.011 to 1.017; albumin, a trace to a cloud; casts, none or occasional granular casts. The urine was the same two years later, just before death. The blood pressure ranged from 180-110 to 265-160 until two days before death, when it fell to 160-90. The phenolsulphonephthalein two years before death was 21 per cent. The total nonprotein nitrogen a week before death was 72 mg. per 100 c.c. The eyegrounds two years before death were normal; both eyes showed cataract. The Wassermann was delayed negative. A week before death the patient became suddenly confused, very weak, with intense headache, dizziness and twitching of the hands. Respiration became Cheyne-Stokes in type and the circulation rapidly failed.

At necropsy there was marked arteriosclerosis and moderate cardiac hypertrophy. The kidneys were very small, red, with very slightly adherent capsule and coarsely granular surface. Histologically, the kidney presented a patchy appearance. In some areas the glomeruli were completely fibrosed and the neighboring tubules collapsed and practically obliterated by fibrous tissue and round cell infiltration. In other areas the glomeruli exhibited moderate cellular proliferation in the tufts, a very little hyalinization of the loops and more or less thickening of the capsules. The neighboring tubules showed for the most part greatly distended lumina; the epithelium was fairly well preserved. A little albuminous precipitate was present in most of the lumina. In these areas there was little interstitial hyperplasia. The medulla exhibited marked fibrosis, with considerable distention of the lumina of the tubules. The vessels showed intense sclerosis.

CASE 28.—*Postinfectious Myocarditis; Early Chronic Nephritis.*

W. W. B., man, aged 36; was admitted Feb. 27, 1917, for dyspnea, cough and insomnia; discharged April 8, 1917, improved.

The patient had had measles, mumps and whooping cough in childhood; typhoid fever at 24. For three months he had had slight dyspepsia, with occasional vomiting after eating. Two months before admission he had an attack of grip. This was followed in a few days by dyspnea, cough, sleeplessness and palpitation on exertion. The day before admission he noticed puffiness of his face. The patient was pallid; lungs emphysematous; heart enlarged, with accentuated second sounds, and slight edema of legs and feet. The urine was a low normal in quantity; specific gravity, from 1.013 to 1.027; albumin, a trace to a cloud; casts, hyaline, sometimes many, sometimes none. The blood pressure gradually rose from 140-87 to 180-125. The blood showed a slight anemia; the Wassermann was negative. The eyegrounds showed some unevenness of the caliber of the vessels; otherwise normal. While under observation the blood pressure rose, but the circulation and urine improved, the dyspnea and edema disappeared and the weight diminished 35 pounds.

Date	Phenolsulphonephthalein	Blood Urea N.	Plasma Chlorids	Plasma CO_2
2/28	42	15	5.9	59
3/21	32			
4/ 2	..	20	5.5	65

The phenolsulphonephthalein on March 21 was estimated just at the end of a week out of the hospital when all the symptoms were exaggerated.

CASE 29.—*Chronic Nephritis; Cardiac Decompensation.*

F. F., man, aged 35; was admitted Nov. 6, 1913, because of edema of legs, palpitation, dyspnea and scanty urine.

The patient had had diphtheria at 9; lead poisoning at 26; typhoid at 27; always subject to colds; had had psoriasis for several years; a moderate daily user of alcohol. Two years before admission he acquired a severe cold on a fishing trip. This was followed by edema of the face and legs, dyspnea, nausea and vomiting and oliguria, lasting a month. The present attack was similar and also followed a fishing trip; it was characterized, in addition, by aching in the lumbar region and moderate diarrhea. On admission he showed a trace of jaundice in the sclerae; marked edema of the legs; badly kept teeth; heart enlarged; a mitral and a basal systolic murmur. The urine ranged from 1,500 to 3,500 c.c.; specific gravity, from 1.011 to 1.023; albumin, a trace to none; casts, from many hyaline and granular to an occasional hyaline. The blood pressure ranged from 145-105 to 132-75. The phenolsulphonephthalein excretion was 50 per cent. The patient lost his edema and 20 pounds in weight in two weeks. He was readmitted Sept. 18, 1916, with the same symptoms, also following a fishing party.

The blood showed a slight anemia; Wassermann negative. The eyegrounds were normal. The urine was from 300 to 1,800 c.c.; specific gravity from 1.017 to 1.021; albumin and casts as before; the blood pressure 160-85 to 135-65.

Date	Phenolsulphone-phthalein	Blood Urea N.	Plasma Chlorids	Plasma CO
9/21.....	50	12	6.0	35
	60	19	5.7	53

During three weeks in the hospital on a salt-free diet, with limited fluid intake, he lost the edema and dyspnea and dropped 30 pounds in weight. A fall in the plasma chlorids is to be noted.

CASE 30.—*Heroin Habitué; Asthenia; Gastro-Enteritis.*

L. C., man, aged 20; was admitted seven months before his death with diarrhea.

The patient had had no previous illness. For at least five months before admission he had been a heroin habitué. For one month he had had diarrhea, nausea, vomiting and intense weakness.

When first seen he had lost 30 pounds in weight; had sclerosed and beaded arteries; a liver slightly enlarged; at times slight edema of the feet. The feces were often frothy, yellowish with much mucus and an abundance of fat; all the duodenal ferments were present. The Wassermann was negative. His blood pressure during the last six months gradually fell from 105-80 to 95-60. His phenolsulphonephthalein output five days before death was 7 per cent. for two hours and his total nonprotein blood nitrogen 55 mg. per 100 c.c. He exhibited a terminal polyuria (4,800 c.c.) with a specific gravity of 1.003; albumin, none or a faint trace. Six months before death he showed no casts, but during the last two weeks hyaline and granular casts were found. The blood was normal; Wassermann, delayed negative. He died with symptoms of collapse.

At necropsy there was found fibrosis of the spleen and pancreas and hypoplasia of the aorta, heart, adrenals and pancreas.

The kidneys were large, pale and flabby, with the capsule adherent at certain points. The pyramids were dark purple. Histologically the glomeruli were normal. The epithelial cells of the tubules, especially the proximal convoluted tubules, showed marked fatty degeneration or infiltration, the majority appearing as "seal-ring" cells.

THE RELATIONSHIP OF THE SO-CALLED IDIOPATHIC CARDIOPATHY TO EXOPHTHALMIC GOITER

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Exophthalmic goiter is usually regarded as a disease dependent on increased or perverted secretion of the thyroid gland. This conception is supported by several facts, among them, that partial removal of the enlarged thyroid not uncommonly serves to mitigate the severity of symptoms, while the administration of thyroid extract intensifies those symptoms which are already present or brings out fresh disturbances of various sorts. Confirmation is also to be had in the fact that the prolonged administration of thyroid extract to dogs and monkeys results in exophthalmos, increased rapidity of the pulse, changes in nitrogenous metabolism, loss of weight and sweating. However true this may be, there are equally good reasons for the belief that alterations in the activity of the thyroid gland are not wholly responsible for the multiplicity of symptoms in exophthalmic goiter, but that other influences are active, such as disturbances in the sympathetic system and, possibly, in the lymphoid tissues, particularly the thymus gland, which, in a certain number of cases of exophthalmic goiter is persistent and apparently flourishing at an age when complete or partial involution is to be expected.

The cardinal symptoms of exophthalmic goiter consist in exophthalmus, tachycardia, tremor and enlargement of the thyroid gland, and recognition of the fully developed picture is often accomplished at a glance. At other times, however, the signs are less obvious and the diagnosis is correspondingly difficult. In this connection the so-called thyroid cardiopathy assumes a place of importance. There are two recognized clinical varieties: first, a cardiopathy due to mechanical interference by the enlarged thyroid, and second, the thyrotoxic heart. The first variety depends on projection of the enlarged thyroid through the upper aperture of the thorax, or on interference with the venous return from the head and neck, and thyroid intoxication, if it enter into the process at all, is sequential and not causative. The thyrotoxic cardiopathy, on the contrary, is regarded as a direct result of disturbances in the thyroid secretion, and, according to some clinicians,

* Submitted for publication Nov. 15, 1917.
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the symptoms associated with it constitute an affection independent of exophthalmic goiter, while others look on them as manifestations of an incompletely developed Graves' disease.

According to Kraus, His and others, the thyrotoxic heart gives rise to two groups of symptoms. In one group the heart beat is increased in frequency, with or without subjective symptoms of palpitation. The pulse varies between 90 and 120 beats to the minute. The carotid pulse sometimes throbs visibly and the patient complains of shortness of breath. Bilateral exophthalmos is seen, but is not common. Unilateral exophthalmos is said to occur rather more frequently, and is associated with pressure of the enlarged thyroid on the corresponding sympathetic ganglion, the pupil is relatively fixed and dilated, and there are inequalities in the temperature of the two sides of the neck. A fine tremor of the fingers may be present. In a second group of cases, in addition to the symptoms just enumerated, the heart shows signs of enlargement.

The cardiopathy of thyrotoxic origin is purely a clinical concept. As far as I have been able to learn, the underlying anatomic changes in the heart and in the thyroid gland have never been determined. In this connection it is to be recalled that pathologic anatomists have long recognized the existence of a lesion characterized by massive enlargement of the heart occurring without valvular or pericardial, arterial, pulmonary or renal changes to account for it — the so-called idiopathic cardiopathy. Six such cases have been encountered in the necropsy room at Bellevue Hospital, and all of them showed naked eye changes in the thyroid gland. In five cases the thyroid was considerably enlarged, and in one case it was diminished in size. Microscopic examination of the thyroid in five of the cases showed the changes incidental to chronic interstitial inflammation with hyperplasia of the colloid vesicles. The sixth could not be examined microscopically. Papillary projections into the alveoli were not found. The colloid content varied in quantity and in its staining reactions. In certain vesicles it was abundant and stained bright red; in others it was pale. In no instance was the size or position of the thyroid such as to interfere mechanically with the action of the heart.

All of the cases were in adult males, the ages being, respectively, 49, 50, 29, 52, 26 and 34 years. The patients were admitted to the hospital with well marked signs of broken compensation in the form of dyspnea and swelling of the lower extremities, the edema sometimes involving the thighs, penis and scrotum. The serous cavities frequently were partially obliterated by collections of fluid. Cough, cyanosis and precordial pain occurred as occasional incidents. With one exception, all of the patients were well nourished. Physical

examination showed great increase in the size of the heart, with or without the association of murmurs. The radial pulse was at times rapid and irregular, at other times slow, having been counted as low as 40 beats to the minute and as high as 160 in the same patient. In two instances in which the blood pressure was recorded the reading was within normal limits, and in all of the cases the artery was described as soft or compressible. In none of the cases were all of the cardinal symptoms of exophthalmic goiter detected. In two cases, however, there was marked bilateral exophthalmos and, in one of these, there was slight swelling of the neck in the region of the thyroid gland, so that only tremor was lacking to complete the picture. At necropsy, five of the subjects showed great enlargement of the heart, and in one instance the heart was described as only slightly enlarged. In five cases the enlargement was due to dilatation and hypertrophy of the several chambers without valvular or pericardial, arterial, pulmonary or renal changes to explain the increase in size. In one case all of the chambers of the heart were dilated and hypertrophied, with the exception of the left auricle; in a second case both auricles were dilated and both ventricles were dilated and hypertrophied; in a third case the right auricle and ventricle were both dilated and hypertrophied, but the left side of the heart was apparently unchanged; in a fourth case both ventricles and the right auricle were dilated and hypertrophied; in a fifth case the right auricle was dilated and both ventricles were dilated and hypertrophied, and, in the remaining case, the right auricle was dilated and both ventricles were dilated and hypertrophied, but in this instance the changes in the left heart were apparently due to valvular lesions, while those of the opposite side could not be accounted for except as part of a thyroid cardiopathy. In four of the cases the endocardium, particularly in the left ventricle, but also in the right ventricle and, occasionally, in the auricles, was diffusely opaque; at other times thickening occurred in patches. In two instances the thickened endocardium extended into the underlying heart muscle for a distance of 2 or 3 mm., and in one case the interventricular septum was the seat of numerous small grayish streaks and patches. In two cases the apex of the left ventricle showed grayish-red, firmly attached mural thrombi, and, in addition, there were thrombotic infarctions in the lungs and kidneys; a third case was marked by thrombosis of the left ventricle near the apex and by hemorrhagic infarctions in the lungs; two of the subjects showed definite anatomic changes incident to syphilis; one subject showed the changes characteristic of well developed status lymphaticus; in one subject the signs of recessive status lymphaticus were present, and, in a third, the thymus was large and fleshlike in appearance, but other indications of status lymphaticus were lacking.

REPORT OF CASES

The clinical and anatomic details of the six cases follow:

CASE 1.—The patient, a man, aged 49, widower, cabinet maker by occupation, was admitted to the medical service of Dr. Robert Carlisle. The patient stated that for the past three years he had suffered at intervals from shortness of breath, palpitation of the heart and precordial pains. The attacks had never been of sufficient severity to incapacitate him for work until about three months before admission, when, in addition to other troubles, he noticed that his feet and ankles were swollen. Later the thighs and scrotum became similarly affected.

Physical Examination.—This showed a well nourished, well developed man, who was in great distress, orthopnea being marked. The area of cardiac dulness was enlarged in all directions. The apex beat of the heart was visible and palpable in the sixth interspace on the left side 13 cm. to the left of the middle line. There were no murmurs. The heart was exceedingly irregular, gallop rhythm being present. The pulse was rapid and irregular, the rate varying between 104 and 128 beats to the minute, once having reached 148. The lower extremities, scrotum and anterior abdominal wall were edematous, and the face was puffy. The specific gravity of the urine was 1.022, it was acid and there was a trace of albumin with a few hyaline and granular casts. The Wassermann reaction was negative. The blood pressure was 158/100 mm. Hg. The non-protein nitrogen of the blood was slightly in excess of the normal, 55 mg. having been found to 100 c.c. of blood. Exophthalmos, tremor and enlargement of the thyroid were not detected. Ophthalmoscopic examination was negative.

Necropsy.—Autopsy 5372. The body was that of a well developed, well nourished man, 49 years of age; weight 180 pounds. There was no exophthalmos and the thyroid was neither palpable nor visibly enlarged. The pretibial tissues were edematous and the abdomen was distended by fluid. The left pleural cavity enclosed a large amount of clear fluid and the lungs were congested and edematous. Scattered through both lungs were numbers of hemorrhagic infarctions, and the smaller branches of the pulmonary artery contained partly attached thrombi.

Heart: The precordial area was enormous. The pericardium enclosed 400 c.c. of clear fluid. The heart was greatly enlarged and weighed 780 gm. The right ventricle was dilated to a marked extent and its walls were hypertrophied, measuring 1 cm. in thickness. The muscular columns within the ventricle were greatly thickened and flattened and numerous delicate whitish streaks were visible in the muscle substance. The conus arteriosus was markedly dilated and its walls were thickened. The right auricle with its appendix was dilated and the musculi pectinati were hypertrophied and flattened, the covering endocardium thickened and opaque. The left ventricle was greatly dilated, the musculature hypertrophied, measuring 2 cm. in thickness; the muscle substance was firm, reddish in color and there were numerous delicate whitish streaks in it, together with fibrotic patches measuring from 0.5 to 1 cm. in diameter. The endocardium of the ventricle was uniformly opaque and thickened. The left auricle was markedly dilated, its walls were thin and the endocardium thickened and lusterless. Near the apex of the left ventricle were several grayish-red thrombi, some of which were attached to the endocardial wall; others were attached to and intercallated among the muscular columns. The valves were normal throughout and the aorta and pulmonary artery were well preserved. The mitral ring was 13 cm. in circumference, the tricuspid 12 cm., with the heart laid open.

The liver was normal in size and reddish brown. The spleen was slightly enlarged, dark red in color, the follicles prominent. The kidneys were slightly enlarged and the capsules stripped easily, leaving behind a brownish-red surface which was perfectly smooth. Both organs showed areas of anemic infarction.

The mucosa of the gastro-intestinal tract was congested and velvety in appearance.

Thyroid: The thyroid was enlarged and weighed 65 gm. It was well contoured, reddish in color and no colloid was visible. On section the cut surface showed numerous delicate, grayish streaks.

Fig. 1 (Case 1).—Heart showing the great thickening of the muscle substance of the conus arteriosus and the rest of the right ventricle, including the muscle columns.

Anatomic Diagnosis.—Marked hypertrophy and dilatation of both hearts; fibrosis of endocardium and of heart muscle; thrombosis of left ventricle; chronic interstitial thyroiditis; pulmonary thrombosis and hemorrhagic infarc-

tion of lungs; chronic passive congestion of viscera; anemic infarction of kidneys; anasarca.

Microscopic Examination.—Tissue was removed from seven different parts of the thyroid gland. The microscopic preparations showed essentially the same changes in all localities. The connective tissue was thickened and irregularly distributed, grouping the vesicles into islands of various shapes and sizes. In places the vesicles were exceedingly small, approximately the size of those in the fetal thyroid. Each vesicle was lined by a single layer of low columnar epithelium and was rounded and empty of colloid. In other islands the vesicles were slightly dilated, and perhaps half of them were filled by colloid which in

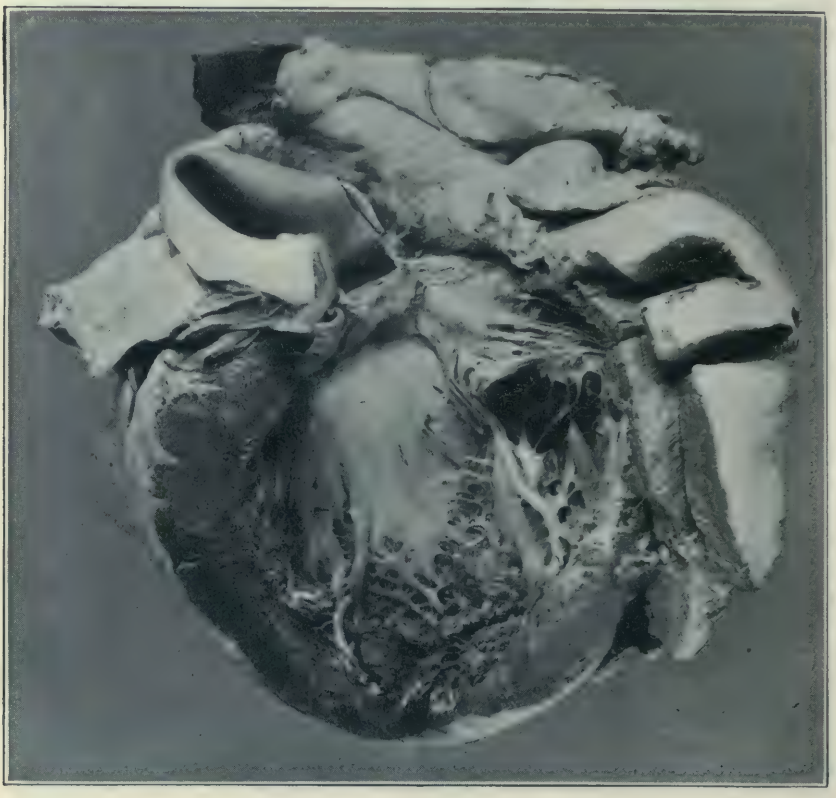

Fig. 2 (Case 1).—Heart showing the immense hypertrophy of the walls of the left ventricle, including the papillary muscles, the diffuse thickening of the mural endocardium, the perfectly preserved valves, and attached thrombi near the apex.

places stained reddish, in other places only faintly pinkish. In still other instances the vesicles were even more dilated and filled by smooth, reddish-staining colloid. Here and there were vesicles which had undergone cystic enlargement and were filled by bright red colloid. All of the vesicles were lined by a single layer of low columnar epithelium and there was no detectable suggestion of papillary infolding in any of them. Lymphoid follicles were not found. The connective tissue was moderately well vascularized.

Microscopic examination of the heart showed slight enlargement of the individual muscle fibers and the nuclei were frequently large and hyperchromatic.

Scattered among the muscle fibers were streaks or patches of moderately cellular fibrillar connective tissue. The vessels were well preserved.

Microscopic examination of the rest of the organs revealed nothing of importance in the present connection.

CASE 2.—The patient, a man, aged 50, was admitted to Bellevue Hospital complaining of shortness of breath and swelling of the lower limbs. While in the hospital the swelling extended upward and involved the penis and scrotum. The apex beat of the heart was neither visible nor palpable, but was located by auscultation in the sixth interspace on the left side near the anterior axillary line. The sounds were of poor quality. There was an apical systolic murmur transmitted toward the axilla. The pulse was rapid and irregular, the rate varying between 54 and 160 per minute. There were numerous moist râles, audible over the entire chest. The urine contained a trace of albumin.

Necropsy.—Autopsy 2903. The body was that of a well developed, well nourished man. The facial hairs were fine in texture. The chest and axillae were almost bereft of hair, and the pubic hairs were sharply defined in a transverse direction. The neck was full and rounded and the thighs were arching. The skin was smooth and delicate. There was nothing to indicate enlargement of the thyroid gland. There was marked edema of the entire body. On opening the thorax the right pleural cavity was found to be full of fluid. There were small, healed tuberculous foci at the apices of both lungs and the lungs were congested throughout.

Heart: The pericardium contained a slight excess of clear fluid. The heart was enormously enlarged and weighed 700 gm. The visceral pericardium was thickened at intervals and numerous small, whitish nodules were scattered along the course of the anterior coronary artery and its branches. Both auriculoventricuar openings were large, admitting four fingers with ease. Both auricles were markedly dilated, especially the left. The cavity of the right ventricle was markedly dilated and its walls were tremendously thickened, the papillary muscles were hypertrophied and flattened and the endocardium showed patches of sclerosis. The left ventricle was dilated, the papillary muscles enlarged and flattened, the endocardium thickened in patches varying from 2 to 10 mm. The wall of the ventricle measured 1.5 cm. in thickness. The valves were normal throughout.

Thymus: There was a small amount of what appeared to be thymic tissue in the fat of the anterior mediastinum. The spleen was small and the follicles were prominent. The intestines showed no lymphoid hyperplasia. The thyroid was enlarged and dark brown in color. The kidneys were congested and the right was the seat of a healed infarction. The liver was congested.

Anatomic Diagnosis.—Dilatation and hypertrophy of both sides of the heart; sclerosis of endocardium; hyperplasia of thyroid; recessive status lymphaticus; chronic passive congestion of viscera; healed infarction of right kidney; anasarca.

Microscopic Examination.—The connective tissue of the thyroid gland was moderately increased in quantity and richly vascularized. In places it occurred as thickened trabeculae, dividing the alveoli into islands of variable size; in other places it could be seen infiltrating its way between individual vesicles, separating them one from the other. Here and there the stroma supported islands of vesicles of the fetal type, each being lined by a single layer of cuboidal epithelium. The vesicles were rounded and empty. For the greater part, however, the alveoli were moderately dilated and filled by pinkish colloid. Papillary projections into the alveoli could not be found.

The heart muscle showed no noteworthy microscopic changes other than slight increase in the size of the individual fibers, marked hyperchromatosis of the nuclei and the presence of small streaks of moderately cellular connective tissue lying among the muscle bundles.

Case 3.—The patient, a man, aged 29, was admitted to the medical service of Dr. Nammack with the statement that, eight months previously, he was suddenly seized with shortness of breath, and that within the past four weeks his feet had become markedly swollen.

Physical Examination.—This showed a well developed man who was extremely dyspneic. There was distinct bilateral exophthalmos. The pulse was rapid, irregular, compressible, and there was visible pulsation in the region of the external jugular veins. The pulse rate never fell below 80, nor did it exceed 104 to the minute. The urine contained a trace of albumin and many hyaline casts. The apex beat of the heart was not visible, but was palpable in the fifth interspace on the left side 1½ inches to the left of the midclavicular line, and was weak and diffuse in character. The area of cardiac dulness was increased about an inch in all directions. There was an apical systolic murmur transmitted to the axilla. Tremor and enlargement of the thyroid were not noted.

Necropsy.—Autopsy 2942. The body was fairly well nourished and moderately muscular. The feet and the subcutaneous tissues of the chest wall were edematous. The abdomen was distended by fluid and both pleural cavities contained about 300 c.c. The lungs were congested. The right apex showed a few small calcified tuberculous foci. The thymus was persistent, in places yellowish, as if replaced by fat; in other places fleshy.

Heart: The pericardium enclosed about 250 c.c. of clear fluid. The heart was slightly enlarged. The right auricle was dilated, its walls were moderately hypertrophied and the endocardium was opaque. The right ventricle was dilated and the trabeculae were hypertrophied and flattened. The conus arteriosus was hypertrophied and dilated. The left ventricle was not hypertrophied, but the endocardium was opaque, as was that of the corresponding auricle. The papillary muscles and chorda tendinae were normal. The valves throughout were well preserved. The aorta was small in caliber and the intima was unchanged. The spleen was small and the follicles visible. The liver and kidneys were congested, as was the mucosa of the gastro-intestinal tract. In the mucosa of the ileum were numbers of somewhat hyperplastic solitary follicles; the agminated patches were not prominent. There were enlarged lymphoid follicles at the base of the tongue and in the mucous membrane of the pharynx. The thyroid was rather small and reddish in color.

Anatomic Diagnosis.—Hypertrophy and dilatation of the right auricle and ventricle; sclerosis of the endocardium; recessive status lymphaticus; chronic passive congestion of viscera; healed tuberculosis of lungs; anasarca.

Microscopic Examination.—The connective tissue trabeculae in the thyroid were numerous, broad, dense and poorly cellular, but richly vascularized, and were so distributed as to divide the thyroid tissue into rounded, oval, oblong or angulated islands made up vesicles, most of which were very small, lined by low cuboidal epithelium without papillary infolding or reduplication, many of them empty. There were moderate numbers of slightly dilated alveoli, some of which enclosed smooth, light pinkish-staining colloid or colloid with a dirty bluish tint.

Microscopic examination of the heart muscle showed no changes worthy of mention at this time.

Case 4.—The patient, a negro man, aged 52, was admitted to the medical service of Dr. Warren Coleman, complaining of shortness of breath on exertion that had been present for three months past. One week before admission the patient noticed that his ankles were swollen. He was subject to severe and frequent cough, with moderate mucoid expectoration.

Physical Examination.—This showed a well nourished man, with marked dyspnea and constant cough. The apex beat of the heart was located 5½ inches to the left of the middle line in the sixth interspace. On the right side dulness extended 1½ inches beyond the edge of the sternum. There was a soft

systolic murmur at the apex that was transmitted to the axilla. The first sound at the base was replaced by a blowing murmur which was transmitted downward. A presystolic murmur and thrill were detected in the tricuspid region. The precordium showed a marked heaving impulse and there was epigastric throbbing. The pulse rate varied between 76 and 108 to the minute. The lower edge of the liver was felt at the level of the umbilicus. The urine contained albumin and a few hyaline casts.

Necropsy.—Autopsy 2388. The body was that of a negro man. There was marked edema of the lower extremities extending up the thighs and involving the scrotum. The heart was markedly enlarged and lay so that the right margin of the ventricle was against the diaphragm. The right side of the heart was greatly dilated and the walls of the right ventricle were hypertrophied. The left ventricle was dilated and its walls thickened. The muscle tissue of the interventricular septum was slightly fibrotic. Both auriculoventricular openings were large, but the valves were normal throughout. The aorta and pulmonary artery were unchanged.

Both lungs were congested. The spleen was small and the interstitial tissues thickened. The kidneys were well preserved, except for small patches of capsular adhesions which, on being stripped away, left behind a slightly granular surface. There was a wedge-shaped, anemic infarction near the outer border of the right kidney. The liver was nutmeg in appearance. The thyroid gland was enlarged and, on section, colloid-containing vesicles were visible.

Anatomic Diagnosis.—Hypertrophy and dilatation of both sides of the heart; fibrosis of the interventricular septum; chronic passive congestion of viscera; anemic infarction of right kidney, hyperplasia of thyroid gland; edema of thighs and scrotum.

Microscopic Examination.—The heart muscle showed patches of hyaline connective tissue scattered here and there, each containing numerous thin walled blood vessels. The endocardium showed considerable fibrosis and hyalinization, few cellular elements being distinguishable. Unfortunately, microscopic examination of the thyroid was not possible, the original preparations together with the material removed at necropsy having been misplaced.

Case 5.—The patient, a man, aged 34, was admitted to the medical service of Dr. Nammack. The patient admitted having had a chancre twelve years previously. Three months before admission he became dyspneic and noticed palpitation of the heart.

Physical Examination.—This showed edema of both legs and cyanosis. The apex beat of the heart was visible and palpable in the sixth interspace on the left side. The right border of cardiac dulness reached 1½ inches to the side of the sternum. There was a systolic murmur at the base and a late diastolic murmur following. The pulse was small, the rate varying between 40 and 130 beats to the minute. Over the apex of the right lung anteriorly there were dulness and crepitant râles. Examination of the sputum, which was blood tinged, showed tubercle bacilli. The urine contained albumin and hyaline and granular casts. The systolic blood pressure was 100. The Wassermann reaction was strongly positive.

Necropsy.—Autopsy 3638. The body was that of a fairly muscular man. The skin was pale and there was moderate edema of the feet and legs and slight swelling in the region of the neck corresponding to the thyroid. The external configuration was unlike that commonly encountered in status lymphaticus. The abdomen was distended by fluid, as were both pleural cavities. The lungs were congested and in the lower lobe of the left lung was a large, hemorrhagic, thrombotic infarction. The upper lobe of the left lung showed numerous patches of fibrosis. The tissues of the anterior mediastinum were edematous and there was a large, symmetrical, bilobed thymus which reached as far downward as the auricles of the heart and upward to the lower level of the thyroid. On section it was pinkish and fleshlike. The precordial area was large.

Heart: The precardium contained an abundance of fluid. The heart was greatly enlarged and weighed 550 gm. The right auricle was dilated, but its walls were not thickened. The right ventricle was hypertrophied, particularly the conus arteriosus, and the ventricle was dilated throughout. The muscular trabeculae were thickened and flattened. The endocardium was thickened and opaque and, on section, whitish threadlike streaks could be seen in the muscular walls for a distance half way through their thickness. The left ventricle was hypertrophied and dilated, the walls measuring 16 to 20 mm. The valves were normal. The liver was nutmeg in appearance. The spleen was small, the trabeculae numerous and prominent and the pulp reddish. The follicles were not visible. The kidneys were congested, but otherwise unchanged. The lymphoid follicles of the intestines were normal.

The thyroid gland was enlarged and weighed 102 gm. The shape was well preserved. On section the gland presented a spongy appearance, due to the presence of numerous small colloid-containing vesicles.

Anatomic Diagnosis.—Hypertrophy and dilatation of both sides of the heart; marked fibrosis of the endocardium of the right ventricle; chronic passive congestion of viscera; persistent thymus; hyperplasia of the thyroid gland; hemorrhagic infarction of the lung; healed tuberculosis; anasarca.

Microscopic Examination.—Running through the thyroid gland in all directions were bands of smooth, dense, noncellular connective tissue from which smaller prolongations penetrated between the alveoli, grouping them into small islands, or surrounding individual alveoli and separating them one from the other. The alveoli varied in both size and shape. Most of them were slightly dilated. All of them were lined by a single layer of cuboidal epithelium and papillary projections into their lumina were not to be found. They were filled with smooth, bright red colloid material. The fibrous trabeculae were well vascularized.

Microscopic examination of the heart showed numerous streaklike or patchy connective tissue foci lying between the muscle fibers, compressing or replacing them.

Case 6.—The patient, a well nourished negro, aged 26, was admitted to the medical service of Dr. Frank Meara with the statement that about a month previously he became short of breath, shortly after which he noticed swelling of the feet and ankles. There was distinct bilateral exophthalmos and slight swelling in the region of the thyroid. The pulse was rapid, varying between 96 and 104 beats to the minute. The apex beat of the heart was located in the sixth interspace, 13 cm. from the middle line on the left side. There was a double murmur at the base and a rough systolic murmur at the apex. The urine contained albumin and many hyaline and granular casts.

The patient furthermore stated that, as a youth, he suffered from frequent "fainting attacks" attended by convulsions and biting of the tongue. These attacks ceased when he was about 14 years of age.

Necropsy.—Autopsy 4340. The body was that of a well nourished negro man. There was marked bilateral exophthalmos and the neck, corresponding to the site of the thyroid gland, presented a slight prominence. The lower limbs were noticeably arched, the axillary hairs were only fairly well developed, the pubic hairs were of the feminine distribution, being sharply defined in a transverse direction, only a few stray hairs stretching toward the umbilicus; the chest was practically hairless, and the glans penis was small. On section, the peritoneal cavity enclosed a slight excess of fluid. Both pleural cavities were similarly bathed; the lungs were large and, on section, showed the characteristic appearances of brown induration. The precordial area was large. The heart was greatly increased in size and weighed 640 gm. The right side was markedly dilated, and the right ventricle was dilated and hypertrophied. The wall of the ventricle measured 0.5 cm. in thickness and the muscular trabeculae in its lumen were thickened and flattened. The left ventricle was hypertrophied.

its wall measuring 15 mm., and the cavity was dilated. The mitral valve was thickened and retracted and there were small numbers of minute vegetations scattered along the line of closure. The aortic valves were thickened and retracted and one of them showed a small pouchlike dilatation. The valves on the right side of the heart were unchanged.

The liver, spleen and kidneys were congested, but otherwise unchanged. The thymus region was occupied by edematous fat and thymic tissue was not to be seen.

The thyroid was enlarged, firm, light reddish in color and only a slight amount of colloid was visible to the unaided eye. On section, both lobes showed innumerable grayish streaks corresponding to connective tissue prolongations. The lymphoid follicles of the intestines were atrophic.

Anatomic Diagnosis.—Dilatation and hypertrophy of both ventricles of the heart, dilatation of the right auricle; sclerosis of the mitral and aortic valves; acute vegetative endocarditis of the mitral valve; bilateral exophthalmos; chronic interstitial thyroiditis; chronic passive congestion of viscera; brown induration of lungs; recessive status lymphaticus; anasarca.

Microscopic Examination.—Tissue removed from different parts of the thyroid gland showed the presence of innumerable large and small, dense, smooth, poorly cellular fibrous trabeculae interspersed among the colloid vesicles in such fashion as to surround almost every individual vesicle. In occasional instances small groups of vesicles of the fetal type were to be seen lying in the connective tissue framework, practically all of them being empty. The great majority of the alveoli were slightly distended, lined by a single layer of very low, almost flattened epithelium, and filled by smooth, pinkish-staining colloid.

Microscopic examination of the lungs showed marked congestion of the blood vessels. Moderate numbers of alveoli contained a few red blood cells and desquamated epithelium and an occasional pigmented phagocyte. Most of the vesicles, however, were unchanged.

In this patient the picture of exophthalmic goiter is almost complete, bilateral exophthalmos, enlargement of the thyroid gland and tachycardia serving to establish the diagnosis with reasonable certainty in spite of the fact that histologic examination of the thyroid gland failed to show the changes customarily found in exophthalmic goiter. The hypertrophy of the left ventricle is undoubtedly to be explained largely on the basis of sclerotic changes in the aortic and mitral cusps. The hypertrophy of the right ventricle and the dilatation of the right auricle are less easily accounted for, the presence of chronic passive congestion of the lungs scarcely serving this purpose. The naked eye and microscopic appearances of the lungs were such as are commonly found in association with valvular defects in the left heart and are to be interpreted as secondary to circulatory disturbances. They are exceedingly common and are never regarded as causative factors in the production of changes in the right heart.

The history of "fainting attacks," convulsions and biting of the tongue occurring in early youth and ceasing at about the fourteenth year is interesting in connection with the bodily configuration and signs of recessive status lymphaticus as revealed by atrophy of the various lymphoid tissues. In these circumstances it is reasonable to assume that the seizures in question were of the nature of anaphylactic

attacks such as are not uncommonly seen in subjects of status lymphaticus, and that cessation of the attacks took place coincidently with completion of involution in the thymus gland and diminution in the lymphoid tissues in other parts. A very considerable percentage of epileptics present the bodily configuration and other signs of status lymphaticus and complete disappearance of the convulsive seizures may be observed as age advances. Microscopic examination of the lymphoid tissues in such subjects shows the presence of innumerable necrotic foci in the germinal follicles, thus releasing nucleoproteins which serve to sensitize the patient. Before the anaphylactic incubation period is at an end another shower of necroses occurs, in this way completing the anaphylactic cycle, the reaction varying in intensity from simple urticarial rashes to convulsive disorders of the epileptiform type or even eventuating in sudden death.

The six cases just synopsized permit of two interpretations — one, that they constitute a clinical and pathologic entity, the other, that the condition is an atypical form of exophthalmic goiter.

Among the arguments in favor of the first mentioned interpretation is that the condition, as observed in Bellevue Hospital at least, occurs only in adult males of a fairly advanced age, whereas exophthalmic goiter is seen most commonly in females below 30 years, and that all of the patients were well nourished, while in exophthalmic goiter there is marked loss of weight due to disturbances in nitrogenous metabolism. The type of histologic change in the thyroid gland lends color to the view that the condition is distinct from exophthalmic goiter, in which, however, the histologic alterations in the thyroid gland are by no means uniform. There is an histologic picture marked by proliferation and dilatation of the vesicles of the thyroid gland, with papillary infolding of the epithelium, that is present in a considerable percentage of all cases of exophthalmic goiter and is apparently otherwise unknown in human pathology. Edmunds and others, however, have shown that if a portion of the thyroid gland be removed from an animal, the remainder, after the lapse of a certain period, exhibits compensatory hyperplastic changes with intravesicular papillary prolongations comparable to those of exophthalmic goiter. A similar condition is found in a certain percentage of stray dogs, and, occasionally, in goats and sheep. Moreover, if such dogs be given iodids in large doses the alveoli again become rounded, the papillary projections disappearing. The administration of iodids, also, is said to prevent the development of intravesicular papillae after operative extirpation of a part of the thyroid. (Marine, Kocher, MacCallum.) On the other hand, the thyroid gland in exophthalmic goiter sometimes shows a histology which is not attended by the changes indicated, but

is characterized by structural deviations not to be distinguished from those of ordinary goiter. In the cases outlined the histologic changes in the alveoli of the thyroid gland were all of the simple, nonpapillary type; that is to say, they were of the sort which may or may not occur in the thyroid in exophthalmic goiter, while the overgrowth of connective tissue was noticeably in excess of that usually encountered in that disease. Thus the microscopic findings do not aid materially in the clinical interpretation. Had it been practicable to make serial sections of the entire thyroid gland in all of the cases, it is possible that intra-alveolar papillae might have been found, thus establishing an histologic composite which, when it does occur, is specific. Finally, the interpretation of these cases as a clinical and pathologic entity is supported by the fact that the increase in the size of the heart is enormously in excess of and different in distribution from that usually encountered postmortem in exophthalmic goiter, in which enlargement is apt to be confined to the left ventricle.

Granting the validity of these arguments, it is none the less difficult to disregard the possibility that the cases under discussion represent examples of atypical, ill developed exophthalmic goiter. Against this view it might be urged, of course, that the changes in the thyroid are incidental and have nothing to do with those in the heart, an objection which appears to be overcome by the observation that the changes in the thyroid are strangely constant for accidental happenings. It might also be urged that the changes in the thyroid are secondary to chronic passive congestion, but sclerosis of the thyroid in these circumstances, if and when it occurs, does not reach the degree shown by the glands under investigation, while sclerotic changes of the same type, extent and distribution are not known in other viscera which have long been the seat of passive congestion. In a case recently examined postmortem at Bellevue Hospital the aortic and mitral valves were greatly thickened and retracted, and the tricuspid valves were reduced to thickened, rounded, cordlike bodies, a degree of sclerosis rarely seen in the valves of the right side of the heart, even in a necropsy service as extensive as that of Bellevue Hospital. The heart was markedly dilated and hypertrophied. In this case the liver was pulsating and there was a jugular pulse, the thyroid was slightly enlarged, weighing 35 gm., and was deeply congested, so that conditions were apparently propitious for atrophy and connective tissue replacement. As a matter of fact, microscopic examination of the thyroid showed innumerable closely packed colloid vesicles without a suggestion of connective tissue overgrowth. However, if one insists on the construction in question and eliminates the thyroid gland as the cause of the enlargement in the so-called idiopathic cardiopathy, one is still left with the extraordinary

combination of an apparently unprovoked dilatation and hypertrophy of the heart associated with symptoms of partially masked exophthalmic goiter, a picture which still is worthy of contemplation from the standpoint of recognition at the bedside. In this connection, also, it is interesting to note that Blum has shown that experimental production of stasis in the thyroid gland results in increased elimination of nitrogen and of inorganic phosphates, and is attended by increased rapidity of the pulse.

CONCLUSIONS

1. The symptomatology of the condition described by clinicians as thyrotoxic cardiopathy is identical with the symptomatology of the lesion familiarly known among pathologic anatomists as idiopathic dilatation and hypertrophy of the heart. The clinical features are characterized by signs of great increase in the size of the heart, with or without murmurs of relative insufficiency and with or without signs of decompensation, as shown by dyspnea, subcutaneous edema, transudation in the serous cavities, cyanosis and the like, by tachycardia, and, on occasions, by bilateral exophthalmos with or without detectable indications of enlargement of the thyroid. Thus the symptoms are largely those of the cardiopathy, and signs of thyroid disturbance, such as tachycardia, tremor, exophthalmos and enlargement of the thyroid, if present, are apt to be projected into the background rather than to assume a prominent place in the picture. Of these symptoms, the tachycardia is constant, and with the patient in bed and at rest, varies between 90 and 160 beats to the minute.

2. Anatomically, the so-called thyrotoxic cardiopathy is characterized by great enlargement of the heart, due to dilatation and hypertrophy of all the chambers or of different combinations of chambers without valvular or pericardial, arterial, renal, pulmonary or other of the causes customarily invoked to explain enlargement of the heart.

3. The so-called thyrotoxic cardiopathy is associated with definite structural alterations in the thyroid in the form of moderate changes in the size of the gland, overgrowth of the fibrous trabeculea, rearrangement of the architecture of the parenchyma, dependent on redistribution of the stroma, regeneration of vesicles and dilatation of the older alveoli, and variations in the amount and staining reaction of the colloid—a chronic interstitial and hyperplastic thyroiditis.

I am extremely indebted to Dr. H. M. Ray for valuable assistance. The photographs are by Mr. William B. Morrison.

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THE EFFECT OF DIURETICS ON THE GENERAL BLOOD PRESSURE IN ANIMALS WITH CONSTRICTION OF THE RENAL ARTERIES *

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Since the days of Traube[1] a mechanical explanation for the high blood pressure of chronic renal disease has frequently been advocated, the original theory postulating increased peripheral resistance in the kidney itself as the cause. Failure of ligature of both renal arteries to raise the blood pressure materially was sufficient disproof of the theory in any such simple form. Various modifications of it have been suggested. Katzenstein[2] obtained a slight rise after incomplete occlusion of the renal arteries, and Alwens[3] by compressing the kidneys in oncometers. In spite of the failure to produce any rise in blood pressure at all comparable to the hypertension of human nephritis, the obvious association of hypertension with those types of renal disease in which the renal arterial system is most compromised, in the absence of any other satisfactory explanation, has prevented the entire abandonment of the mechanical theory. Furthermore, clinicians have always been impressed with the compensatory nature of hypertension.

The following experiments were undertaken in the hope of affording further light on the tenability of Traube's theory under conditions of increased functional demand on the kidney. It was thought possible that, if the renal artery were narrowed, but not occluded, and then diuretic substances administered intravenously, the compensatory nature of hypertension might be revealed. Narrowing of the renal artery without obliteration was made possible by the aluminum band of Halsted.[4] The diuretic substances used were sodium chlorid, urea and caffein, injected intravenously; in addition, the effect of epinephrin was tested. With an aluminum band placed about the renal artery, no increased flow through the kidney can occur as a result of mere local vasodilatation. If any reflex mechanism exists whereby diuretic substances can produce an increased flow through the kidney under these conditions, a rise in general blood pressure must occur. If, on the other hand, no rise in general blood pressure and no diuresis fol-

* Submitted for publication Dec. 10, 1917.

* From the Hunterian Laboratory of the Department of Medicine of the Johns Hopkins University.

1. Gesammelte Abhandlungen, Berlin, 1856, **2,** 290; **3,** 440.
2. Virchows Arch. f. path. Anat., 1905, **182,** 327.
3. Deutsch. Arch. f. klin. Med., 1910, **98,** 137.
4. Bull. Johns Hopkins Hosp., 1905, **16,** 346.

lows, then the evidence for this particular view of the compensatory nature of hypertension would be lacking.

TECHNIC OF EXPERIMENTS

The experiments were performed as follows: As large a dog as obtainable was used and was anesthetized with paraldehyd. A cannula was then placed in the carotid artery and connected with a recording mercury manometer for the registration of the arterial pressure, and another cannula placed in the femoral vein for the injection of the solutions. The kidneys were next delivered through lumbar incisions and the renal arteries exposed. A cannula was inserted in the left ureter and connected with an electrical drop recorder. In Experiments 1 to 11 no further operative procedures were done at this time, but in Experiments 12 to 15 the right renal artery was now ligated.

A control period was then begun, arterial pressure and urine flow being recorded on a kymograph. When the blood pressure had become steady, the various solutions were injected into the femoral vein, a sufficient time being allowed to elapse between injections for the blood pressure curve to return to its former level, varying from ten minutes to one hour in different experiments. The speed of injection was as nearly uniform as possible. The aluminum band was then placed around the left renal artery with sufficient constriction to reduce markedly the pulsation distal to it, but not to abolish pulsation completely. In Experiments 1 to 11, ligature of the right renal artery was also performed. This operation sometimes required the administration of a small amount of ether.

After a second control period, the various solutions were again injected through the femoral cannula in the same volume and the same order as before. The dog was killed at the conclusion of the experiment before recovering from the anesthetic.

The solutions tested, and the volumes used, were as follows:

5 per cent. sodium chlorid solution, 10 to 20 c.c.
5 per cent. urea in 0.9 per cent. sodium chlorid solution, 10 to 20 c.c.
5 per cent. caffein solution 7.5 to 10 c.c.
1 in 50,000 epinephrin chlorid solution, 10 c.c.

The amount injected varied with the size of the dog. In the bulk of the experiments 15 c.c. of the sodium chlorid and of the urea solutions, and 10 c.c. of the caffein and the epinephrin solutions were used.

The experimental difficulties in adjusting the band so as to diminish, but not completely obstruct, the blood flow were considerable. A number of experiments had to be abandoned because of failure to accomplish this, or because of clotting in the cannula, or death of the dog before the conclusion of the tests. In addition, one of us (E. W. B.) was called to active military duty before sufficient experiments had been performed, and the other (K. H.) must assume the responsibility for the later experiments and for the opinions expressed in this paper.

In order to bring the results together in a clear manner, the blood pressure and urine-drop records have been measured on the tracings, and the figures from the eight successful experiments are given in tabular form. The blood pressure figures give the rise, represented by +, or fall, represented by —, in mean carotid pressure expressed

in mm. Hg. The urine is calculated as drops per hour, because of the extremely scanty secretion obtained in parts of the experiment. The two lines, before and after, refer to the observations made before the constriction of the left renal artery with the band, the right renal artery having been ligated previously.

TABLE 1.—Data of Experiments

Experiment Number	Control Period: Urine, Drops per Hr.	Sodium Chlorid		Urea		Caffein		Adrenalin	
		Bl. Pr. Change in Mm. Hg	Urine, Drops per Hr.	Bl. Pr. Change in Mm. Hg	Urine, Drops per Hr.	Bl. Pr. Change in Mm. Hg	Urine, Drops per Hr.	Bl. Pr. Change in Mm. Hg	Urine, Drops per Hr.
2 Before.....	60	.....	....	.....	....	Sl. variations	420	+60	180
After.....	12	.... .	....	.....	....	Unchanged	10	+40	15
8 Before.....	20	+2	20	+2	20	—6	20	+40	60
After.....	8	+2	8	+2	8	—5	8	+25	8
10 Before.....	60	+3	60	+2	60	—12	180	+23	120
After.....	6	+10	6	+2	6	—15	6	+25	6
11 Before.....	60	+10	120	+4	120	—20	360	+17	240
After.....	120	+7	240	+2	150	—15	120	+12	120
12 Before.....	40	+6	140	+4	180	—20	240	+12	180
After.....	30	+6	43	+3	45	—5	30	+14	30
13 Before.....	60	Sl. variations	180	Sl. variations	120	—27	420	+25	540
After.....	150	Sl. variations	180	Sl. variations	240	—32	600		
14 Before.....	90	+3	240	+3	240	—25	480	+20	300
After.....	150	Sl. variations	360	+3	360	—30	150	+19	150
15 Before.....	15	+5	60	+5	60	—25	45	+20	60
After.....	28	Sl. variations	60	Sl. variations	90	—15	60	+15	28

As may be seen at a glance, the results of these experiments as shown in the table are negative. They give no support to the view that hypertension in chronic renal disease is a compensatory mechanism, brought into play when the renal arterial stream-bed is narrowed, by chemical or reflex paths, to counteract the effect on excretion of the locally diminished blood flow. Their value is only that of negative evidence in general. They do not disprove the compensatory nature of hypertension, but show that its demonstration is not to be had by the experimental method employed. A similar study of animals in whom a constricting band had been left for a considerable period around the renal artery, simulating a chronic lesion, would be of interest, but external events prevented our undertaking it, as had been hoped.

It gives us great pleasure to thank Prof. Theodore C. Janeway for his directions throughout the course of the experiment.

CONTRIBUTION TO THE PHYSIOLOGY OF THE STOMACH

XLVI. GASTRIC SECRETION DURING FEVER

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Beaumont[1] was first to observe that

> In febrile diathesis or predisposition from whatever cause . . . the villous coat becomes red and dry, at other times pale and moist and loses its smooth and healthy appearance; the secretions become greatly vitiated, greatly diminished, or entirely suppressed, and mucous coat scarcely perceptible, the follicles flat and flaccid, with secretions insufficient to protect the nervous papillae . . . When there are corresponding symptoms of disease, as dryness of the mouth, thirst, accelerated pulse, etc., no gastric juice can be extracted, not even on the application of alimentary stimulus. Drinks received are immediately absorbed or otherwise disposed of, none remaining in the stomach ten minutes after being swallowed. Food taken in this condition of the stomach remains undigested for twenty-four to forty-eight hours or more, increasing the derangement of the whole alimentary canal and aggravating the general symptoms of disease.

Clinical and experimental evidence confirms these early observations of Beaumont. Thus Gluzinski,[2] 1888, noted that not only is there a diminution of the quantity of gastric juice, but that during the entire duration of an infectious fever the gastric juice showed an absence of acid, and that with the cessation of fever, or somewhat later, acid reappeared. During chronic fevers there was no apparent diminution of acid; Gluzinski therefore concluded that the diminution of gastric juice was less influenced by elevation of temperature than by infection.

Sassecki[3] noted that the quantity of acid was not always diminished during fever, and that if dyspepsia was present before the onset of fever, it in itself might be the cause of the diminished secretion.

Uffelman,[4] in an analysis of the vomitus of eight children during fever, always found a diminished secretion of gastric juice.

Grünfelder,[5] in a series of experiments on two dogs, observed the effect of infection on gastric juice by means of the Pawlow pouch.

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* Submitted for publication Dec. 1, 1917.

* From the Hull Physiological Laboratory of the University of Chicago.

1. Beaumont, W.: Experiments and Observations on the Gastric Juice and Physiology of Digestion, 1833.
2. Gluzinski, L. A.: Deutsch. Arch. f. klin. Med., 1888, **42**, 145.
3. Sassecki: Cited from Gluzinski, Footnote 2.
4. Uffelman: Die Diët in den acute fieberhaften Erkrankungen, 1877.
5. Grünfelder: Ztschr. f. exper. Path. u. Therap., 1914, **16**, 141.

Gastric secretion was markedly reduced in quantity; free and total hydrochlorid were also reduced; pepsin remained constant.

Nichols[6] says there is usually a diminution or total suppression of hydrochloric acid in various fevers, while pepsin is apparently little reduced.

Stockton[7] says that "the examinations of stomach contents in fever patients yield contradictory results and consequently are not always easily interpreted. The secretion may be but little impaired; more often there is a deficiency in hydrochloric acid, with less deficiency in the secretion of ferments.

It is thus seen that most observers report a diminished gastric secretion and a lowered acidity in fevers.

We have undertaken to renew the study of the changes in gastric secretion during fever in order to determine the mechanisms involved in the changes.

Procedure.—We prepared a number of dogs with Pawlow accessory stomachs. A period of ten days to three weeks was allowed each dog for recovery before we commenced our work.

The dogs were fed a standard quantity (from 150 to 200 gm.) of cooked meat and as much water as desired. The gastric juice was then collected at hourly intervals for five hours. In addition, the juice was collected one hour before feeding. The temperature of the animal was taken hourly during the period of secretion and the next morning following the experiment, so that we were sure that we were dealing with normal dogs.

Analysis of Gastric Juice.—One c.c. of the total quantity of gastric juice secreted was titrated on the same day for free and total hydrochloric acid. *Pepsin* was determined by diluting 1 c.c. of gastric juice with 10 c.c. tenth-normal hydrochloric acid and the amount of digestion calculated by the Mett's method.

Chlorids.—Van Slyke's method was followed, but we used 1 c.c. of gastric juice because we found that during fever the quantity of juice secreted was so small as to necessitate the use of small amounts in our determinations.

I. CHANGES IN GASTRIC SECRETION PRODUCED BY FEVER

Procedure.—The experiments were conducted as follows: Gastric juice was collected for one hour to obtain the amount of the continuous secretion; at the end of this period the temperature was recorded.

An intravenous injection of either sodium nucleate (10 c.c. of a 10 per cent. solution) or of killed culture of *B. prodigiosus* was then given, and after five or ten minutes the animal was given from 150 to 200 gm. of meat. At times the animal would refuse to eat. On such occasions forced feeding was resorted to, the meat being placed on the back of the tongue. With each meal 150 c.c. of water was given.

In several instances it was noted that the dogs vomited the food about one and one-half hours after the injection of the nucleate or the *B. prodigiosus.* When this occurred, the food, which was always undigested, was fed to the animal again.

6. Nichols: Am. Jour. Med. Sc., 1911, **142,** 93.
7. Stockton, C. G.: Diseases of the Stomach, New York, 1914, p. 217.

RESULTS

The results are briefly summarized in the accompanying Table 1, and Figure 1, A and B.

Table 1 shows that in a series of experiments conducted on three dogs the changes produced in the gastric secretion were remarkably constant. The volume was reduced. Thus, with normal temperature the volume was 27, 30 and 85.5 c.c. in Dogs 2, 5 and 10, respectively. In fever, with temperature of 105 F., the volume was reduced to 10.4 c.c., 5.5 c.c. and 7.1 c.c.

Total acid and free acid were markedly reduced.

Pepsin was increased in two dogs, and diminished in one. The increase is apparently dependent on volume.

Chlorids are practically constant. We wish to emphasize this fact here in striking contrast to the change in the total and free acid. The secretion is mucous and ropy in character.

We may, therefore, conclude from the foregoing that during fever there are definite changes in the gastric secretion which are chiefly a diminution of volume, diminished free and total hydrochloric acid, a percentage increase in pepsin, and a nearly constant percentage of chlorids. We wish to note that these changes are present only during the febrile period, and that the next morning, the animals' temperature being normal, the gastric secretion was again normal.

It is worthy of special emphasis that the injection of sodium nucleate or *B. prodigiosus* produces marked disturbances in addition to elevation of the temperature. Thus diarrhea, mucous and bloody stools occurred in most of the dogs. Severe chills and severe prostration were often present, yet the following day the temperature was normal, the animal apparently well and the flow of gastric secretion normal. Only when our control experiments showed a return to normal did we repeat the experiment on the same animal.

The fact that in five experiments on one dog a killed culture of *B. prodigiosus* produced results identical with those following sodium nucleate indicates that there is nothing in the drugs or toxins used which might interfere or alter gastric secretion, but that it is the fever and its reaction which are the basis of the results.

II. MECHANISM INVOLVED IN THE CHANGES OF GASTRIC SECRETION DURING FEVER

(*a*) *Rôle of Heat or Temperature Elevation.*—In a recent communication by Meyer and Carlson[8] the effect of external heat was proved to be a factor in the depression of hunger contractions. Salle,[9] by elevat-

8. Meyer & Carlson: Am. Jour. Physiol., 1917, **44.**

9. Salle: Verhandl. d. 28 Versamml. d. Gesellsch. f. Kinderh., 1911, **72**; Jahrb. f. Kinderh., **74,** 627.

TABLE 1.—SUMMARY OF EXPERIMENTS AND CONTROLS ON THREE DOGS, SHOWING THE EFFECT OF FEVER ON GASTRIC SECRETION

Hr.	Dog 2, Fed a Standard Diet of 130 Gm. Meat				Dog 5, Fed a Standard Diet of 200 Gm. Meat				Dog 10, Fed a Standard Diet of 200 Gm. Meat			
	Normal Av. 7 Exper.		Fever* Av. 5 Exper.		Normal Av. 8 Exper.		Fever* Av. 9 Exper.		Normal Av. 7 Exper.		Fever† Av. 5 Exper.	
	Temp. F.	Vol. C.c.	Temp. F.	Vol. C.c.	Temp. F.	Vol. C.c.	Temp. F.	Vol. C.c.	Temp. F.	Vol. C.c.	Temp. F.	Vol. C.c.
1	101.9	6.7	104.5	1.8	101.7	7.3	104.9	0.9	101.5	24.0	104.8	1.3
2	101.8	6.3	106.1	2.2	101.6	6.6	105.5	0.9	101.4	19.8	105.9	1.4
3	101.9	5.2	105.7	2.1	101.7	6.1	105.4	1.0	101.5	16.6	105.6	1.3
4	102.0	4.7	105.1	2.6	101.7	5.4	105.3	1.3	101.6	13.1	104.8	1.9
5	101.9	4.1	103.7	1.7	101.8	4.6	104.1	1.3	101.5	11.9	104.4	1.2
Total.....		27.0	.....	10.4	....	30.0	.....	5.5	.....	85.5	.....	7.1
Total acid....	0.3854%		0.1039%		0.4272%		0.1422%		0.4968%		0.0350%	
Free acid....	0.3151%		0.0209%		0.3610%		0.0699%		0.4345%		None	
Pepsin...	1.85 Mm.		2.64 Mm.		1.90 Mm.		3.10 Mm.		2.3 Mm.		1.8 Mm.	
Chlorids.	0.495% Cl.		0.480% Cl.		0.511% Cl.		0.459% Cl.		0.495% Cl.		0.416% Cl.	

* Injection of sodium nucleate.
† Injection of B. prodigiosus.

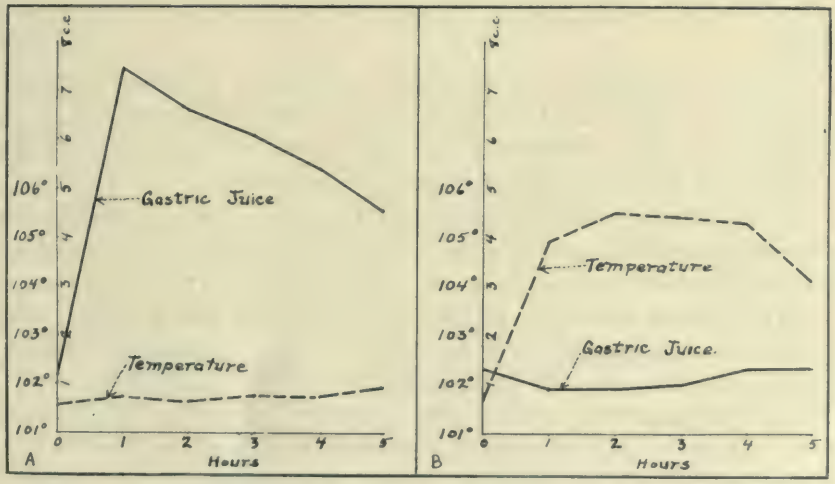

Fig. 1.—*A*, Composite chart of eight experiments (on Dog 5) showing the volume of gastric juice secreted after a meal of 200 gm. of boiled meat. Temperature normal.

B, Composite chart of nine experiments (on Dog 5) showing changes in gastric secretion during fever produced by injection of sodium nucleate or *B. prodigiosus.* Food, 200 gm. boiled meat.

ing the external temperature, produced a condition simulating diarrhea in young dogs and reports a diminished volume; diminished free and total acid of the gastric juice. Salle fed his animals milk only, and therefore his results are not conclusive.

We determined the effect of elevating the temperature of the dogs by external heat, employing the method used by Meyer and Carlson.[8] By using a stronger electric current we were able to obtain a temperature in the cage varying from 45 to 64 C.

The normal temperature was first recorded, the animal placed in the hot box for one hour and the juice collected; at the end of this period the dog was fed. The animal was kept in the box for two hours longer, the juice being collected separately each hour. The animal was then removed to the room and the gastric juice collected for two hours at normal room temperature. A series of three experiments on one dog were thus conducted.

RESULTS

Table 2 and Figure 2, A and B, show the marked alteration in the character of the gastric secretion produced by elevating the temperature of the dog by means of external heat. The results are almost identical with the results produced by fever itself. A very striking fact is the entire absence of secretion on removal of the animal from the hot box, even though the body temperature fell rapidly to normal. The gastric secretion was normal again within twenty-four hours.

The animal becomes extremely prostrated for one to two hours after an exposure in the hot box. Restlessness, dyspnea, rapid pulse and extreme exhaustion are present. Salivation is pronounced, and this is a striking feature when compared with the decrease in gastric juice.

We may therefore conclude that temperature elevation produced by external heat induces the same changes in gastric secretion as are produced by fever, experimental or infectious. This is probably the condition of gastric secretion in cases of sunstroke.

(*b*). *Effect of Fever Syndrome.*—Does the fever or temperature elevation complex abolish the psychic factor, impair the function of the secretagogues or depress the gastric gland cells directly?

The striking similarity of the results obtained during actual fever and in the experiments of temperature elevation caused by external heat at once suggests the possibility of the entire change being due to failure of the psychic factor. Thus Pawlow[10] says that "in the occasional illness of our experimental animals there is an augmented or a diminished activity of the peptic glands as contrasted to the normal," and he believes that the change in the secretion is "of a reflex nervous nature." We are able at present to differentiate between the psychic and the chemical factors by the use of gastrin.[11] When gastrin is

10. Pawlow: The Works of the Digestive Glands, 1910, p. 241.
11. Keeton and Koch: Am. Jour. Physiol., 115, **37,** 481.

TABLE 2.—Summary of Experiments (with Controls) on the Influence of Thermic Fever on Gastric Secretion

Hour	Dog 2.—Fed a Standard Diet of 200 Gm. Meat				
	Normal Average 8 Experiments		Fever Average 3 Experiments		
	Body Temperature, F.	Volume Gastric Juice, C.c.	Body Temperature, F.	Volume Gastric Juice, C.c.	Temperature of Box, C.
1	101.6	7.3	106.6	1.3	48
2	101.7	6.6	108.5	0.4	47
3	101.6	6.1	105.9	0.1	45
4	101.7	5.4	103.9	None	21
5	101.8	4.6	103.0	None	21
Total	.....	30.0	.....	1.8	
Total acid.....	0.4272%		0.2066%		
Free acid.....	0.3610%		0.0942%		
Pepsin.....	1.90 Mm.		2.6 Mm.		
Chlorid.....	0.511% Cl.		0.472% Cl.		

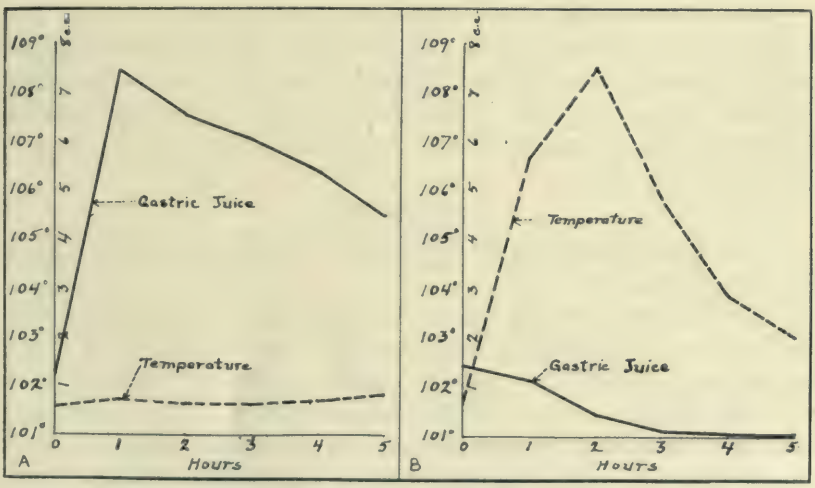

Fig. 2.—*A*, Composite chart of eight experiments (on Dog 5) showing the volume of gastric juice secreted after a meal of 200 gm. of boiled meat. Temperature normal.

B, Composite chart of three experiments on Dog 5, showing change in volume of gastric juice during temperature elevation caused by external heat. Food, 200 gm. boiled meat.

injected subcutaneously it gives rise to a definite secretion of gastric juice, in which the psychic factors play no rôle at all. We therefore employed gastrin to determine the direct response of the gastric glands during fever.

Procedure.—We first determined the normal response of our animals to subcutaneous injection of 1 c.c. of gastrin. Having secured our normals we determined the gastrin action during fever. Our procedure was generally as in the preceding experiments. The dog was allowed to secrete normally for one hour (continuous secretion), then sodium nucleate or *B. prodigiosus* was injected intravenously. At the end of the second hour 1 c.c. of gastrin was injected subcutaneously. The juice was then collected at hourly intervals for from three to four hours after the injection of gastrin. In some cases no analysis of the chlorids was made because of the small quantity of secretion.

In studying the effects of temperature elevation due to external heat on the secretion caused by gastrin, we employed the methods detailed on page 358, with the addition that 1 c.c. of gastrin was injected.

RESULTS

In a series of five experiments on two dogs in which fever was produced by nucleate and prodigiosus, and in twelve experiments on five dogs, in which a temperature elevation as high as from 105 to 112 was caused by external heat, the changes produced in the secretion caused by the injection of 1 c.c. of gastrin were striking and uniform. The volume was diminished; at times there was no secretion at all. The total and free acid were reduced. The chlorids were practically constant (Tables 3 and 4, Figs. 3 and 4, A and B).

These experiments prove that during fever produced by the injection of sodium nucleate or *B. prodigiosus,* or during temperature elevation caused by external heat, gastrin is unable to induce the normal secretion of gastric juice. The changes in the gastrin secretion are exactly the same as those found in the gastric juice secreted in response to food during fever.

DISCUSSION

What other factor must be considered in the alteration of gastric secretion during fever?

Salle[9] believed that the heat of the body itself was the most important factor. Grünfelder[5] considers the temperature of the blood together with the secretogogues as equally important. Pawlow[10] holds that the changes are of a reflex nervous nature. Our experiments demonstrate beyond doubt the fact that the heat of the body is an important factor in causing an alteration in gastric secretion.

Furthermore, since, as we have proved that gastrin when injected subcutaneously during fever is unable to induce its normal secretion, it follows that any gastrin formed from the food substances eaten during fever would also be unable to induce a gastric secretion. Our results with gastrin point to a definite depression of the gastric gland cells,

which may be explained by the action of "toxins" elaborated during fever. It is conceivable that the toxins present might have a direct action on the glands. We believe that the greatest factor in the alteration of gastric secretion during fever is a change in the cells of the glands of the stomach. We are inclined to this view because of our

TABLE 3.—Summary of Experiments (with Controls) on Two Dogs, Showing the Effect of Injection of 1 C.C. Gastrin on the Secretion of Gastric Juice During Fever

	Hour	Temperature, F.	Volume, C.c.	Total Acid, per Cent.	Free Acid, per Cent.	Chlorids, per Cent.	Pepsin, Mm.	Remarks
Dog 5.—Normal; secretion produced by 1 c.c. gastrin. Average 3 experiments	1	101.4	15.6	0.4771	0.4314	.....	1.0	Clear
	2	101.4	5.3	0.5044	0.4557	0.499	1.1	Clear
	3	101.5	1.6	0.3312	0.2188	.....	1.4	Clear
	4	101.6	1.1	.....	.....	.....	...	Clear
Total.....	...	.....	23.6					
Dog 5. — Fever; secretion produced by 1 c.c. gastrin. Average 2 experiments	1	106.2	0.6	0.0912	None	0.431	4.3	Mucus
	2	105.6	1.0	0.1824	0.0639	.....	3.3	Mucus
	3	104.8	1.2	0.1915	0.0406	.....	4.6	Mucus
	4	103.4	0.5	.....	.....	.....	...	Mucus
Total.....	...	.....	3.3					
Dog 9.—Normal; secretion produced by 1 c.c. gastrin. Average 3 experiments	1	101.6	18.9	0.4497	0.3889	0.477	1.7	Clear
	2	101.3	13.8	0.4770	0.4132	.....	1.2	Clear
	3	101.4	4.7	0.2764	0.1395	.....	2.4	Clear
	4	101.6	1.9	.....	.....	.....	...	Clear
Total.....	...	.....	39.3					
Dog 9. — Fever; secretion produced by 1 c.c. gastrin. Average 3 experiments	1	105.6	1.4	0.0517	None	0.451	4.0	Mucus
	2	105.3	2.4	0.0669	None	.....	3.5	Mucus
	3	104.6	1.5	0.0726	None	.....	4.2	Mucus
	4	103.5	1.0	.....	.....	.....	...	Mucus
Total.....	...	.....	6.3					

results with gastrin. Although the mechanism of the action of gastrin is not definitely understood, recent work would seem to indicate that it has a direct action in the cells of the gastric glands. Thus in a personal communication from Luckhardt, Koch and Keeton on "Effect of Atropin on Gastric Stimulation of Stomach," they have noted that, "any dose of atropin sufficient to inhibit gastric flow under food stimulation will reduce the secretory activity following gastrin stimulation.

It is always possible, however, even after maximal doses of atropin, doses that are definitely toxic to the animal, to cause a flow of juice by increasing the dose of gastrin." These findings tend to confirm our view. We suggest that in fever gastrin is unable to induce its normal gastric secretion because of alteration in the gland cells. We believe that the same mechanism explains the failure of gastric secretogogues

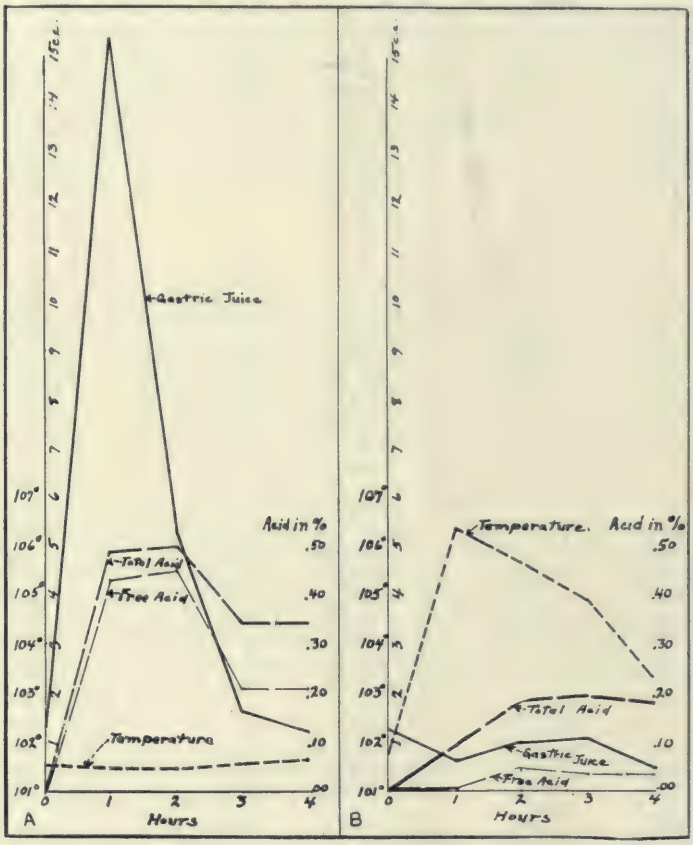

Fig. 3.—*A,* Composite chart of three experiments showing character of secretion produced by injection of 1 c.c. gastrin subcutaneously, during normal temperature.

B, Composite chart of two experiments showing character of gastric secretion produced by gastrin during fever caused by sodium nucleate and *B. prodigiosus.*

produced by food eaten during fever to cause a secretion. The most important factor in the alteration of gastric secretion during fever is a depression of the gland cells. These cell changes are transitory in character, and are probably in the nature of a cloudy swelling.

TABLE 4.—Summary of Experiments (with Controls) on Five Dogs, Showing the Effect of Injection of 1 C.c. Gastrin on the Secretion of Gastric Juice During Thermic Fever

	Hour	Body Temp.,* F.	Volume, C.c.	Total Acid, per Cent.	Free Acid, per Cent.	Pepsin, Mm.	Chlorids, per Cent.	Box Temp., C.	Remarks
Dog 11.—Normal; secretion produced by 1 c.c. gastrin.	1	101.6	14.1	0.4102	0.3190	1.6	0.480	25	Clear
	2	101.6	7.0	0.4193	0.3281	1.8	.....	..	Clear
Average 2 experiments	3	101.5	3.7	0.2232	0.0912	2.7	.....	..	Clear
Total.....	...	.....	24.8						
Dog 11. — Fever; secretion produced by 1 c.c. gastrin; dog in hot box.	1	109.8	1.9	0.2275	0.1294	3.8	0.465	52	Mucus
	2	101.5	0.7	0.1201	0.0401	2.5	.....	24	Mucus
Average 5 exper.	3	100.6	0.7	0.0851	None	3.0	.....	24	Mucus
Total.....	...	.....	3.3						
Dog 12.—Normal; secretion produced by 1 c.c. gastrin.	1	101.2	11.0	0.5082	0.4417	1.3	0.504	23	Clear
	2	101.3	7.1	0.5287	0.4603	1.7	.....	..	Clear
Average 4 experiments	3	101.3	3.5	0.3669	0.2621	2.0	.....	..	Clear
	4	101.2	1.0	.....	.....	...	.....	..	Clear
Total.....	...	.....	22.6						
Dog 12. — Fever; secretion produced by 1 c.c. gastrin; dog in hot box.	1	109.2	2.9	0.3341	0.1456	2.6	0.489	49	Mucus
	2	105.2	0.6	0.1884	0.0144	2.8	.....	42	Mucus
Average 3 experiments	3	102.8	0.5	0.0638	None	...	.....	24	Mucus
	4	102.2	0.2	.....	.....	...	.....	24	Mucus
Total.....	...	.....	4.2						
Dog 9.—Normal; secretion produced by 1 c.c. gastrin.	1	101.6	18.9	0.4497	0.3889	1.7	.....	..	Clear
	2	101.3	13.8	0.4770	0.4132	1.2	0.477	21	Clear
Average 3 experiments	3	101.4	4.7	0.2764	0.1395	2.4	.....	21	Clear
	4	101.6	1.9	.....	.....	...	.....	..	Mucus
Total.....	...	.....	39.3						
Dog 9. — Fever; secretion produced by 1 c.c. gastrin; dog in hot box.	1	108.9	0.8	0.3322	0.2092	3.1	.....	42	Mucus
	2	106.7	0.4	0.2462	0.1094	...	.....	46	Mucus
Average 2 experiments	3	104.5	0.1	.....	.....	...	.....	42	Mucus
	4	101.5	0.0	.....	.....	...	.....	20	
Total.....	...	.....	1.3						
Dog 14.—Normal; secretion produced by 1 c.c. gastrin.	1	100.0	26.3	0.4371	0.3873	1.2	.....	..	Clear
	2	100.3	9.0	0.4288	0.3691	1.2	.....	23	Clear
Average 2 experiments	3	100.2	1.0	0.1823	0.0866	2.4	.....	25	Clear
	4	100.3	0.7	.....	.....	...	.....	23	Mucus
Total.....	..	.....	37.0						

* The fever was produced by elevating the external temperature by use of a hot box.

TABLE 4.—Summary of Experiments (with Controls) on Five Dogs, Showing the Effect of Injection of 1 C.c. Gastrin on the Secretion of Gastric Juice During Thermic Fever—
(*Continued*)

	Hour	Body Temp.,* F.	Volume, C.c.	Total Acid, per Cent.	Free Acid, per Cent.	Pepsin, Mm.	Chlorids, per Cent.	Box Temp., C.	Remarks
Dog 14. — Fever; secretion produced by 1 c.c. gastrin; dog in hot box.	1	109.0	0.7	0.3372	0.1824	3.1	.....	35	Mucus
	2	105.1	0.6	0.1368	None	4.0	.....	40	Mucus
	3	103.4	0.1	.....	.....	...	.....	45	Mucus
Average 1 experiment	4	102.5	0.0	.....	.....	...	.....	24	Mucus
Total.....	...	.....	1.4						
Dog 16.—Normal; secretion produced by 1 c.c. gastrin.	1	101.3	20.0	0.4740	0.4122	1.7	.....	..	Clear
	2	101.4	20.7	0.5013	0.4466	1.8	.....	23	Clear
Average 3 experiments	3	101.4	17.7	0.4922	0.4375	1.9	.....	23	Clear
	4	101.4	11.2	0.4588	0.4132	1.7	.....	23	Clear
Total.....	...	.....	69.6						
Dog 16. — Fever; secretion produced by 1 c.c. gastrin; dog in hot box.	1	109.9	1.2	0.1641	0.0821	2.5	.....	48	Mucus
	2	103.2	0.3	0.1732	0.0274	...	.....	26	Mucus
	3	102.2	0.0	.....	.....	...	.....	25	
Average 1 exper.									
Total.....	...	.....	1.5						

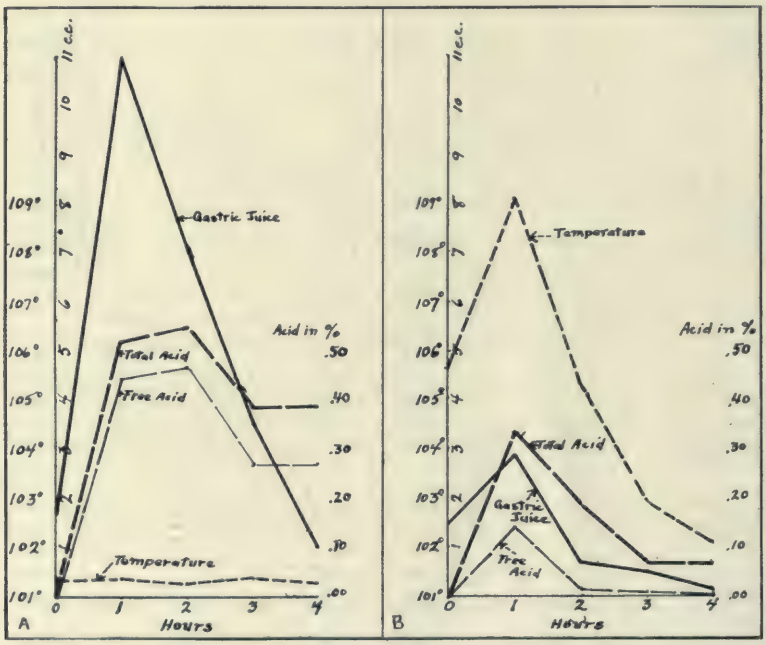

Fig. 4.—*A*, Composite chart of four experiments on Dog 12, showing character of secretion produced by subcutaneous injection of gastrin.

B, Composite chart of three experiments on Dog 12, showing character of secretion produced by gastrin during temperature elevation caused by external heat.

In view of the marked changes in gastric secretion in fever, these studies should be extended to other digestion secretions, especially those of the pancreas and the intestinal mucosa.

SUMMARY

1. During fever gastric secretion is diminished in volume and in total and free acid. The percentage of chlorids is constant or only slightly reduced and pepsin is relatively increased. The secretion is ropy and mucous in character.

2. External heat itself when sufficient to induce temperature elevation of from 2 to 4 F., will cause the same changes in gastric juice as produced by fever.

3. Gastrin is unable to induce a secretion of gastric juice during fever, as well as in a condition of temperature elevation due to external heat.

4. It is suggested that during fever, toxins are elaborated having a direct depressor action on the cells of the stomach so that they fail to react to the secretory nerve impulses and to the secretogogues.

We wish to thank Dr. F. C. Koch for his kindness in furnishing us with the gastrin preparations used in our experiments.

INFLUENCES OF EXTRARENAL FACTORS ON THE RENAL FUNCTIONAL TEST MEAL*

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FACTORS INFLUENCING TEST MEALS

Seeking to investigate renal function in both healthy and diseased kidneys in terms of their response to their most accustomed stimulation, Hedinger and Schlayer[1] studied their reaction to a twenty-four-hour standard diet. Mosenthal,[2] continuing this method, revised their procedure and made it somewhat more adaptable to private practice and nonhospital patients. His dietary contained about 13.4 gm. of nitrogen, 8.5 gm. of salt, and 1,760 c.c. of fluid, including a fair quantity of diuretic materials in the form of purins. The twenty-four-hour diet was given in three meals: at 8 a. m., 12 m. and 5 p. m. The urine was collected at two hour intervals from 8 a. m., to 8 p. m., and a night specimen from 8 p. m. to 8 a. m. of the following day; but no three day fixed diet was demanded preceding the last day, as was suggested by Hedinger and Schlayer. Furthermore, Mosenthal felt there was no essential need for following out exactly the kind of meal he outlined, if only the subject partook of his three accustomed meals a day, took no food or drink between them, and followed the directions given for the collection of urine.

This procedure proved to be, in his opinion, an excellent one for the test of renal function. His normal subjects returned two-hour urinary specimens that varied 10 points in specific gravity between the highest and the lowest (later 9 points were accepted as the minimum normal variation). And the night urine was 1.018 or more in specific gravity with its nitrogen concentration above 1 per cent. and a total volume of 400 c.c. or less. The quantitative excretion of nitrogen, salt and water approximated the intake. With a renal function impairment, the earliest change appeared in the night urine; the quantity increased, the specific gravity lowered and the nitrogen concentration was reduced. Severe functional derangement manifested itself by a much lowered and constantly fixed specific gravity in all specimens and a diminished output of nitrogen, salt and water. Later, Mosenthal

* Submitted for publication Dec. 20, 1917.

* From the Harriman Research Laboratory and the Pathologic Laboratory of the Roosevelt Hospital.

1. Hedinger and Schlayer: Deutsch. Arch. f. klin. Med. 1914, **114,** 120.
2. Mosenthal: THE ARCHIVES INT. MED., 1915, **16,** 733.

and Lewis[3] in comparing several of the approved tests for renal function, namely, the phenolsulphonephthalein, nonprotein nitrogen and urea content of the blood, Ambard coefficient of urea excretion and the test meal, found the latter to be the most sensitive, in that it was relatively the first to disclose any degree of renal inefficiency.

Aware of the possibilities of the influence of extrarenal factors on the test meal reaction, we undertook to study the degree of uniformity of response to the test meal by the same individual, the extent to which a lack of such uniformity might interfere with unqualified interpretations of the results, and to disclose, if possible, extra renal factors that may have operated to produce such variations in reactions. All our subjects were persons going about their duties and leading their accustomed lives. They were fed a standard diet, approximating that outlined by Mosenthal at a special diet kitchen, associated with the Laboratory of Roosevelt Hospital. Each took the test meal for two, three or more days, usually consecutively, and carried out with care the instructions as to the collection of urine and abstinence from food and drink between meals.

As concluded by Mosenthal, and too, as a result of our experiments (which already include over 200 test meals) variations in the specific gravity of the two-hour specimen of urine, and the volume and character of the night specimen, appear to be an index to the state of renal function, as elicited by the test. The reaction of the kidney to the stimulus of the food given in the test meal truly represents the reaction for which the test was conceived and shows the actual renal factors involved in the reaction. Influences from other sources serving to significantly affect the specific gravity variations, the volume or the nitrogen concentration of the night specimen must be looked at as complicating extrarenal factors. The variations in specific gravity of the two-hour urinary specimens are functions of both the volume of fluid and amounts of solids excreted during each period, and it is quite apparent that extrarenal influences on one or the other of these factors can influence the periodic specific gravity variations.

As for the excretion of water, the skin and lungs as well as the kidneys are excretory organs. The loss of water from the body surface is subject to the physical laws which govern water evaporation and serves definite purposes. Hence the influence on such fluid loss of atmospheric temperature, humidity and rate of air circulation. This loss of water is a vehicle for the dissipation of body heat and is a factor in the mechanism for regulation of body temperature. The remarkable constancy of body temperature in health stamps the mechanism of its regulation, and thus the operation of its several factors, as exceedingly

3. Mosenthal and Lewis: Jour. Am. Med. Assn., 1916, **67,** 933.

persistent. It is thus accorded priority over less persistent body functions and fluid supplied the kidneys for excretion must be secondary to the demand made at that time on the body fluids by the temperature-regulating mechanism.

Investigating with the calorimeter the question of water excretion, Rubner[4] found that at a constant atmospheric temperature the water loss by skin was directly proportional to the relative humidity; an increase of water loss with an increase of atmospheric temperature; and further, that about 21 per cent. of body heat produced was dissipated by water evaporation. Gephart and Du Bois[5] estimated the amount to be in the neighborhood of 24 per cent. Wolper and Peters,[6] studying the daily curve of water excretion through skin and lungs, found that it was not influenced by the time of day, as such, but was at a minimum during the late night hours or the day hours of sleep. In other words, it was at a minimum when metabolism was at a minimum. Further, the intake of food had no influence on the curve of excretion. They found an average excretion of 70 gm. of water per hour at 24 C., and 65 per cent. relative humidity when the air was still. Laschtschenko,[7] investigating the effect of water intake on water excretion from skin and lungs, found that it exerted no influence whatever. To summarize then: water loss by skin and lungs takes precedence over excretion by kidney; it is lowest when metabolism is lowest; it is not influenced by the intake of food or fluids and under ordinary circumstances must be nearer a liter (in the active man) than the 400 c.c. allowed by Mosenthal.[2, 8] The fluid supply to the kidney consequent to such a preferential demand by the skin is gaged by the condition of water balance of the body, which, in turn, is manifestly influenced by the water intake.

The reactions of Subjects S and B given in Tables 1 and 2, illustrating the tendency of the responses of most of our subjects to the test diet when taken for a few consecutive days, show a tendency toward concentration and reduction in the range of variations in

4. As quoted by A. J. Kalman, Pfluger's Arch. f. Physiol., 1906, **112,** 561.

5. Gephart, F. C., and Du Bois, E. F.: The Archives Int. Med., 1916, **17,** 902. The exact percentage of total heat given up to evaporation of water as found by an investigator is of course greatly influenced by the physical condition prevailing in the colorimeter, temperature, relative humidity and rate of air circulation.

6. Wolpert and Peters: Arch. f. Hyg., 1906, **60,** 299.

7. Laschtschenko: Arch f. Hyg. 1898, **33,** 145.

8. Assuming 2,500 calories for the daily metabolism of a fairly active individual, and allowing a heat dissipation via water evaporation as equivalent to 25 per cent. of the total metabolism, the actual water production in such a case would be as per calculation as follows: 25 per cent. of 2,500 cal. = 625 cal.; 0.6 cal. for evaporation of 1 c.c. H_2O: $\frac{625}{0.6}$ = 1,041 c.c. H_2O.

TABLE 1.—Showing Urinary Reaction on a Test Diet.

Student S., aged 22; laboratory assistant in good health.

Date	Volume, C.c.	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm.	Per Cent.	Gm.	Per Cent.
12/6/16						
8 - 10 a.m.	140	1.022				
10 - 12 m.	265	1.020				
12 - 2 p.m.	420	1.014				
2 - 4 p.m.	354	1.012				
4 - 6 p.m.	146	1.018				
6 - 8 p.m.	194	1.016				
Total day.....	1,519		7.10	0.47	11.4	0.75
Total night, 8 p. m. – 8 a. m.	340	1.026	3.69	1.00	3.35	0.99
Total 24 hours.....	1,859		10.79		14.75	
2/5/17						
8 - 10 a.m.	105	1.022				
10 - 12 m.	200	1.020				
12 - 2 p.m.	156	1.022				
2 - 4 p.m.	154	1.023				
4 - 6 p.m.	187	1.021				
6 - 8 p.m.	242	1.016				
Total day.....	1.044				7.10	0.68
Total night, 8 p. m. – 8 a. m.	540	1.018			3.60	0.66
Total 24 hours.....	1.584				10.70	
2/6/17						
8 - 10 a.m.	80	1.020				
10 - 12 m.	135	1.021				
12 - 2 p.m.	330	1.016				
2 - 4 p.m.	180	1.024				
4 - 6 p.m.	130	1.025				
6 - 8 p.m.	175	1.022				
Total day.....	1,030		8.6	0.83	6.7	0.65
Total night, 8 p. m. – 8 a. m.	380	1.024	2.7	0.72	2.5	0.65
Total 24 hours.....	1,410		11.3		9.2	
2/7/17						
8 - 10 a.m.	105	1.022				
10 - 12 m.	175	1.022				
12 - 2 p.m.	185	1.024				
2 - 4 p.m.	165	1.024				
4 - 6 p.m.	120	1.026				
6 - 8 p.m.	335	1.015				
Total day.....	1,085		12.0	1.1	7.1	0.65
Total night, 8 p. m. – 8 a. m.	610	1.016	6.8	1.1	4.2	0.70
Total 24 hours.....	1,695		18.8		11.3	

TABLE 1.—Showing Urinary Reaction on a Test Diet—(*Continued*)

Date	Volume, C.c.	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm.	Per Cent.	Gm.	Per Cent.
2/8/17						
8 - 10 a.m.	60	1.025				
10 - 12 m.	108	1.026				
12 - 2 p.m.	156	1.023				
2 - 4 p.m.	126	1.025				
4 - 6 p.m.	100	1.027				
6 - 8 p.m.	131	1.025				
Total day.....	681		4.8	0.70	2.2	0.66
Total night, 8 p. m. - 8 a.m.	325	1.025	2.5	0.77	2.1	0.65
Total 24 hours.....	1,006		7.3		4.3	
2/9/17						
8 - 10 a.m.	72	1.027				
10 - 12 m.	60	1.028				
12 - 2 p.m.	98	1.029				
2 - 4 p.m.	94	1.029				
4 - 6 p.m.	120	1.029				
6 - 8 p.m.	132	1.025				
Total day.....	576		5.1	0.89	4.1	0.70
Total night, 8 p. m. - 8 a. m.	400	1.027	5.1	1.27	2.6	0.60
Total 24 hours.....	976		10.2		6.7	

The subject complained very much of thirst the last two days of the test. On the single day (December 6) there was a variation of specific gravity from 1.012 to 1.022, 10 points. Beginning with February 5, the variations between maximum and minimum for five consecutive days are 7, 9, 11, 4 and 4 points.

specific gravity of the two-hour specimens. The total fluid output fell steadily from day to day (2, 7, 17, Table 1 excepted) and the sodium chlorid elimination fell likewise. The nitrogen excretion was not definitely interfered with by the progressive tendency toward oliguria. This change in response of the kidney appears in spite of the identical stimulus to the kidney of food and fluid intake. In general terms, such reactions as these are explained as due to an effort on the part of the body to prevent depletion of its fluids in order to keep constant the concentration of its solids. It is difficult to explain what factors operated in any particular day's reaction to compel conservation of body fluids. This conservation might have been due to excessive preferential demand for water by the skin, resulting from a marked increase in metabolism or exposure to atmospheric temperature and relative humidity most favorable for water evaporation. On the other hand, the volume of fluid ingested may have been too low for the subject or

the solid intake too high. When these latter factors are operating the concentration and fixation of specific gravity would become progressively more marked as the test days went on, as illustrated by the cases just outlined; then again, the test meal might have been given at a time when the tissues were in a state of fluid depletion. In all events, it appears that the water balance of the body is in a state of apparently

TABLE 2.—URINARY REACTIONS ON A TEST DIET

Subject B, aged 25; physician on house staff in good health.

Date	Volume, C.c.	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm.	Per Cent.	Gm.	Per Cent.
2/13/17						
8 - 10 a. m.	120	1.026				
10 - 12 m.	160	1.025				
12 - 2 p. m.	216	1.024				
2 - 4 p. m.	128	1.020				
4 - 6 p. m.	104	1.029				
6 - 8 p. m.	85	1.031				
Total day	813		6.7	0.82	6.1	0.75
Total night, 8 p. m. - 8 a. m.	303	1.029	3.8	1.2	2.1	0.68
Total 24 hours	1,116		10.5		8.2	
2/14/17						
8 - 10 a. m.	82	1.028				
10 - 12 m.	102	1.026				
12 - 2 p. m.	109	1.029				
2 - 4 p. m.	120	1.028				
4 - 6 p. m.	99	1.030				
6 - 8 p. m.	70	1.028				
Total day	582		6.3	1.1	7.9	1.3
Total night, 8 p. m. - 8 a. m.	276	1.031	3.9	1.4	1.0	0.36
Total 24 hours	858		10.2		8.9	
2/15/17						
8 - 10 a. m.	74	1.029				
10 - 12 m	55	1.030				
12 - 2 p. m.	124	1.028				
2 - 4 p. m.	70	1.029				
4 - 6 p. m.	80	1.033				
6 - 8 p. m.	49	1.031				
Total day	452		6.1	1.4	3.4	0.74
Total night, 8 p. m. - 8 a. m.	342	1.031	5.2	1.5	2.5	0.74
Total 24 hours	794		11.3		5.9	

The specific gravity variations for the three consecutive days are 11, 4 and 5 points.

fine adjustment in the healthy individual, and this balance the body strongly seeks to maintain. Nor is it difficult to appreciate how the effort to preserve such a balance will, in a great measure, influence the maximum specific gravity in the test meal reaction, as well as the maximum variation therefrom.

Table 3 discloses the interesting fact that with the successive reduction of the total twenty-four-hour volume of urine there was a tendency toward a percentile increase of the night volume, or, in other words, a tendency toward a constancy of night volume in spite of successive diminutions in daily total volumes. It is to be recalled in this connection that water loss from the skin is at a minimum during the sleeping hours and consequently there is relatively more water available to kidney for excretion during that time. An extrarenal factor

TABLE 3.—Showing Percentile Increase of Night Over Day Volume

Date	Subject S.						Subject B.		
	12/6	2/5	2/6	2/7	2/8	2/9	2/13	2/14	2/15
Total day vol. c.c.....	1,519	1,044	1,030	1,085	681	576	813	582	452
Total night vol. c.c...	340	540	380	610	325	400	303	276	342
Total 24-hr. vol., c.c..	1,859	1,584	1,410	1,695	1,006	976	1,116	858	794
Percentile ratio of total night to 24-hour volume.....	18	34	27	36	32	41	27	32	43

of a different order which will be mentioned later, however, may be the contributory cause in the test day of Feb. 7, 1917, of Subject S., where the night volume equaled 56 per cent. of the total twenty-four-hour volume. It is pertinent to recall in this connection the findings of Quincke,[9] who, in studying the urinary output of subjects who were not ill of nephritis, found that the average hourly output of the early morning hours (from 5 to 8 a. m.) was far greater than that for the twenty-four hours or the total night hours. To what extent, we may ask, did the minimum loss of water by skin and lungs during the night render possible the availability of fluids for the kidney at a time so removed from the last hours of water intake?

Mosenthal recognized the tendency toward a fixation of specific gravity at a high concentration in healthy subjects with oliguria, and allows for it in a measure by taking the highest specific gravity of the day as a basis for estimating the normal variations in the urine of subjects taking the test meal.

9. Quincke, H.: Arch. f. Exper. Pathol., 1877, **7**, 115.

It is well known that exposure to cold and chilling of body surface induce an increased flow of urine. The causes of this phenomenon are apparently not identical in every instance and probably vary in particular cases. Several factors may have operated in the production of the diuresis. In the first place, the chilling of the body surface may have caused a constriction of surface vessels, secondary to which splanchnic dilatation to some degree, including renal vessels, might occur. Secondly, the peripheral vasoconstriction shuts off water loss by evaporation from the skin, thereby allowing an increase of fluids at the disposal of the kidney. Thirdly, one must consider the possibility of the response of the kidney through a nervous mechanism with the stimulation of the skin by cold as the source of the afferent impulse.

Jungman[10] demonstrated by cerebral stimulation in animals that this nervous mechanism was not merely the expression of a vasomotor reaction, as shown by the character of the urine during the diuretic period. This latter fact had not been studied by Ashner and Bechterew, who, prior to Jungman, had investigated diuresis produced by cerebral stimulation. Jungman, keeping his animals on a fixed diet and comparing the urine of control days and immediate foreperiods with the period immediately following cerebral stimulation, found that the urine of the diuretic period contained an increase of sodium chlorid, due both to an increase in volume and in concentration, this at times reaching tenfold that of the control period and even exceeding at times the chlorid concentration in the blood. Furthermore, separate specimens of urine drawn off at different times during a single diuretic period showed the volume and sodium chlorid concentration to be mutually independent. The absolute nitrogen output was found to be fairly constant. All these findings were independent of water intake, which was determined by control experiments. Jungman, on the basis of these results, suggested that the stimulation of the renal epithelium might be a factor, and that vasomotor reaction was not the only phenomenon to explain the result of this nerve stimulation.

The reactions of Subject O., as given in Table 4, show how chilling of the body surface can affect the test meal reaction.

On the first day, Feb. 13, 1917, the heating apparatus was shut off in the laboratory, and Subject O. feeling uncomfortably cold all day, passed a total day volume of 1,864 c.c. as against 847 c.c., 1,103 c.c. and 672 c.c. on the three subsequent days. With this as the probable extrarenal factor, the diuresis was practically continuous all day, the specific gravity varying at the most 5 points, though the concentration was correspondingly lower. Again, on the night of the third test day, Feb. 15, 1917, after walking an hour and a half in the cold, he passed

10. Jungman: München. med. Wchnschr., 1913, **2**, 1760.

TABLE 4.—Showing How Reaction is Affected by Chilling of Body Surface

Subject O, aged 25; laboratory assistant in good health.

Date	Volume, C.c.	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm.	Per Cent.	Gm.	Per Cent.
2/13/17						
8 - 10 a. m.	286	1.017				
10 - 12 m	238	1.015				
12 - 2 p. m.	322	1.020				
2 - 4 p. m.	310	1.020				
4 - 6 p. m.	430	1.017				
6 - 8 p. m.	278	1.016				
Total day.....	1,864		9.30	0.50	14.1	0.76
Total night, 8 p. m. – 8 a. m.	630	1.019	5.2	0.80	4.3	0.68
Total 24 hours.....	2,494		14.5		18.4	
2/14/17						
8 - 10 a. m	74	1.024				
10 - 12 m.	118	1.027				
12 - 2 p. m.	135	1.025				
2 - 4 p. m.	184	1.025				
4 - 6 p. m.	138	1.027				
6 - 8 p. m.	198	1.023				
Total day.....	847		12.0	1.4	6.3	0.75
Total night, 8 p. m – 8 a. m.	280	1.029	4.8	1.7	2.0	0.70
Total 24 hours.....	1,127		16.8		8.3	
2/15/17						
8 - 10 a. m.	50	1.025				
10 - 12 m.	194	1.020				
12 - 2 p. m.	133	1.020				
2 - 4 p. m.	340	1.021				
4 - 6 p. m.	138	1.019				
6 - 8 p. m.	248	1.015				
Total day.....	1,103		9.3	0.84	8.4	0.76
Total night, 8 p. m. – 8 a. m.	790	1.016	5.6	0.70	6 0	0.76
Total 24 hours.....	1,893		14.9		14.4	
2/16/17						
8 - 10 a. m	72	1.026				
10 - 12 m.	98	1.024				
12 - 2 p. m.	125	1.025				
2 - 4 p. m	163	1.020				
4 - 6 p. m.	86	1.027				
6 - 8 p. m.	128	1.029				
Total day.....	672		9.2	1.37	5.1	0.76
Total night, 8 p. m. – 8 a. m.	290		5.6	1.92	1.9	0.64
Total 24 hours.....	962		14.8		7.0	

about 500 c.c. of his total night specimen of 790 c.c. at 10.30 p. m. For the four test meals, the absolute nitrogen elimination for the twenty-four hours was relatively constant, both in the total night and day specimens, and as a necessary corollary the nitrogen concentration varied inversely as the volume. The sodium chlorid concentration throughout the period was very constant; the increased volume not reducing, but showing rather a tendency toward increasing it. The sodium chlorid output varied considerably, therefore, with the fluctuations in the volume of urine. These urinary findings coincide with those of Jungman in the diuretic specimens, resulting from the stimulation of the fourth ventricle. The influence of cold must be considered; for it can interfere considerably with the correct interpretation of the test meal. Even as an influence for part of the day it will increase or decrease the maximum variation of the specific gravity, depending on whether the specific gravity of the specimens outside the period of its operation were high or low. At night, especially, if the room is cold and the subject happens to throw off some of the coverings during sleep, thus exposing the body surface, the urinary findings may be identical with those described by Mosenthal as the earliest signs of impairment of renal function. Influence on the renal nervous mechanism by emotional states could affect the reactions in a similar way.

Subject P., aged 44. Her symptoms had been headache, dyspnea and weakness. Hemoglobin 78 per cent.; blood pressure 165/110; eyegrounds, slight arteriosclerosis. Phenolsulphonethalein output, Feb. 14, 1917, 58 per cent. in two hours. Blood picture, Feb. 14, 1917, nonprotein nitrogen 42, creatinin 0.96, uric acid 3.8 mg. per 100 c.c. The urine showed a faint trace of albumin and a few hyaline casts, with negative findings on several examinations.

Subject T., aged 45, had complained of occasional headache and dyspnea. Blood pressure 165/110. Blood picture, March 5, 1917, nonprotein nitrogen 28, urea 32, creatinin 1.5, and uric acid 4.0 mg. per 100 c.c. The urine showed a trace of albumin and many hyaline and granular casts.

Of the group of subjects with definite renal involvement we submit the reactions of two who previous to the test were on restricted diets for several months and who at the time of the tests were subjectively free of any symptom consequent to renal insufficiency. We are here afforded an opportunity to observe the effect of dietary treatment on renal function as evidenced by this test, and, what is more to our present purpose, the influence on the degree of reliability of the test meal findings with the omission of the fixed diets for the several days preceding the test as suggested by Hedinger and Schlayer.

Though no specific effort was made to investigate the effect of a previous dietary, the response of Subjects P. and T. to the test meal add further data to the discussion of nitrogen excretion in nephritics having difficulty with nitrogen elimination. They had been put on a diet low in nitrogen and high in fluids, drinking usually a gallon of

TABLE 5.—Reactions of Subject P.

Date	Volume, C.c.	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm.	Per Cent.	Gm.	Per Cent.
2/13/17						
8 - 10 a. m.	236	1.009				
10 - 12 m.	290	1.012				
12 - 2 p. m.	285	1.011				
2 - 4 p. m.	120	1.020				
4 - 6 p. m.	134	1.017				
6 - 8 p. m.	58	1.023				
Total day	1,223		4.4	0.36	7.7	0.63
Total night, 8 p. m. - 8 a. m.	240	1.023	2.4	0.99	1.6	0.68
Total 24 hours	1,463		6.8		9.3	
2/15/17						
8 - 10 a. m.	25	1.030				
10 - 12 m.	65	1.020				
12 - 2 p. m.	46	1.023				
2 - 4 p. m.	74	1.020				
4 - 6 p. m.	171	1.018				
6 - 8 p. m.	58	1.025				
Total day	439		4.3	0.98	3.2	0.73
Total night, 8 p. m. - 8 a. m.	888		4.1	0.46	6.5	0.74
Total 24 hours	1,327		8.4		9.7	
2/16/17						
8 - 10 a. m.	71	1.019				
10 - 12 m.	130	1.017				
12 - 2 p. m.	93	1.022				
2 - 4 p. m.	90	1.018				
4 - 6 p. m.	110	1.019				
6 - 8 p. m.	71	1.027				
Total day	565		4.5	0.79	4.1	0.73
Total night, 8 p. m. - 8 a. m.	350	1.021	3.1	0.90	2.6	0.75
Total 24 hours	915		7.6		6.7	
2/20/17						
8 - 10 a. m.	166	1.017				
10 - 12 m.	65	1.021				
12 - 2 p. m.	82	1.020				
2 - 4 p. m.	85	1.022				
4 - 6 p. m.	128	1.022				
6 - 8 p. m.	124	1.025				
Total day	650		4.5	0.75	4.2	0.70
Total night, 8 p. m. - 8 a. m.	590		4.0	0.68	4.1	0.69
Total 24 hours	1,240		8.5		8.3	

water a day. This was continued until the test meals were given. The reactions for the first day appear comparatively normal in both, allowing for the results that follow oliguria in Subject T. In the successive test days, however, the findings correspond to the reaction of interstitial nephritics—an increased night volume, reduced nitrogen concentration (except that of Feb. 16, 1917, Table 5). They show on all days, however, nitrogen retention. The absolute nitrogen outputs show a fair degree of constancy for each of the consecutive days, and

TABLE 6.—Reaction of Subject T.

Date	Volume, C.c.	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm.	Per Cent.	Gm.	Per Cent.
3/5/17						
8 - 10 a. m.	40	1.024				
10 - 12 m.	36	1.028				
12 - 2 p. m.	96	1.026				
2 - 4 p. m.	46	1.024				
4 - 6 p. m.	76	1.027				
6 - 8 p. m.	90	1.025				
Total day	384		5.5	1.4	4.0	1.05
Total night, 8 p. m. - 8 a. m.	240		4.0	1.7	2.2	0.92
Total 24 hours	624		9.5		6.2	
3/6/17						
8 - 10 a. m.	78	1.023				
10 - 12 m.	168	1.019				
12 - 2 p. m.	164	1.021				
2 - 4 p. m	304	1.015				
4 - 6 p. m.	114	1.014				
6 - 8 p. m.	292	1.018				
Total day	1,120		6.4	0.62	7.6	0.74
Total night, 8 p. m. - 8 a. m.	495		3.8	0.72	4.0	0.81
Total 24 hours	1,615		10.2		11.6	
3/7/17						
8 - 10 a. m	72	1.023				
10 - 12 m.	50	1.019				
12 - 2 p. m.	98	1.023				
2 - 4 p. m.	121	1.019				
4 - 6 p. m.	76	1.022				
6 - 8 p. m.	108	1.025				
Total day	525		4.9	0.93	5.2	1.0
Total night, 8 p. m. - 8 a. m.	670		3.9	0.58	6.7	1.0
Total 24 hours	1,195		8.8		11.9	

TABLE 7.—Summary

Name and Date	Maximal Specific Gracity	Maximal Variation	Night Urine				
			Volume, C.c.	Specific Gravtiy	Nitrogen per Cent.	Per Cent. Above or Below 400 C.c.	Per Cent. Above or Below 1% N Concentration
Normal							
Subject S.							
12/6	1.022	10	340	1.026	1.0	—15	0
2/5	1.023	7	540	1.018	....	+35	
2/6	1.025	9	380	1.024	0.72	—5	—28
2/7	1.026	9	610	1.016	1.1	+53	+10
2/8	1.027	4	325	1.025	0.77	—19	—23
2/9	1.029	4	400	1.027	1.27	0	+27
Subject O.							
2/13	1.025	8	590	1.015	0.68	+48	—32
2/14	1.027	4	280	1.029	1.7	—30	+70
2/15	1.025	5	790	1.017	0.7	+98	—30
2/16	1.029	9	290	1.029	1.93	—27	+93
Subject D.							
3/ 5	1.025	18	315	1.023	1.1	—21	+10
3/ 6	1.021	14	210	1.027	1.2	—48	+20
3/20	1.019	13	375	1.019	0.93	—6	—7
3/21	1.020	16	320	1.022	1.15	—20	+15
3/22	1.023	19	285	1.025	1.3	—38	+30
Chronic Interstitial Nephritis							
Subject G.							
3/14	1.021	7	460	1.013	0.74	+12	—26
3/15	1.023	8	668	1.015	0.84	+67	—16
3/16	1.030	5	618	1.021	1.20	+55	+20
Subject P.							
2/13	1.023	14	240	1.023	0.99	—40	—1
2/15	1.027	9	888	1.010	0.46	+112	—54
2/16	1.027	10	350	1.021	0.90	—13	—10
2/20	1.025	8	590	1.015	0.68	+48	—32
Subject T.							
3/5	1.028	4	240	1.024	1.7	—40	+70
3/6	1.023	10	495	1.015	0.76	+24	—24
3/7	1.025	6	670	1.017	0.58	+68	—42
Subject L.							
2/28	1.029	15	899	1.010	0.67	+125	—33
3/ 1	1.024	7	760	1.014	0.90	+90	—10
3/ 2	1.028	2	590	1.020	1.2	+48	+20

an equal degree for the day and night specimens when their eliminations are separately considered. The constancy appears to be one of total rather than of percentile elimination. Thus, Subject T., having difficulty with nitrogen elimination, can concentrate nitrogen as high as 1.7 per cent. in night specimens, and Subject P., as high as 0.99 per cent. Such variations in nitrogen concentration can appear, then, in the urine of individuals who have difficulty with nitrogen elimination, and it seems possible that a long continued diet low in nitrogen and high in fluids might have enabled them to respond quite normally, for one day anyway, to the renal test meal, though no concomitant power for increased total nitrogen elimination is evident.

A fair index of the reliability of any judgment based on a single test meal reaction in active individuals, healthy, or with slight, though definite, renal involvement, can be gathered from Table 7. Degrees of variations of specific gravity between maximum and minimum fluctuate markedly, and the variations do not necessarily diminish with the increase of maximum specific gravity, but may be quite the reverse (Subject D.). The night volumes, too, show decided fluctuations, varying, as in Subject O., from 98 per cent. above 400 c.c. to 27 per cent. below it on the following day. The nitrogen concentration of the night specimen shows a similar tendency to vary significantly above and below 1 per cent. (Subject T.); and the higher nitrogen concentration may occur with the specimen of lowest specific gravity (Subject S., Feb. 7, 1917). Finally, the range of variation of the composite test meal reactions is quite sufficient to enable one, by selective comparison, to demonstrate at times, on the basis of the accepted method of interpretation, the better reaction for the poorer kidney.

SUMMARY

The kidney is called on during the course of a day to respond to many influences other than the stimulus of ingested food.

Such extraneous influences are extrarenal factors affecting the test meal reaction.

Some of the factors we have been able definitely to identify, such as (1) the effect of the state of water reserve of the tissues, and (2) the chilling of the body surface.

These factors can function significantly to distort the test meal reaction when viewed in the terms suggested by Mosenthal.

When so functioning they affect chiefly the fluid element in the test meal reaction complex; and this mainly by virtue of the fact that the skin and lungs make a preferential and significant demand on body fluids, whereas the excretion of solids by the skin and lungs is practically negligible.

These varying extrarenal influences are sufficient to require judgment with reservation as to renal functional efficiency on the basis of the suggested method of test meal interpretation, especially:

1. On the basis of a single test meal (unless the reaction gives evidence of marked renal insufficiency).

2. In individuals who are well enough to be about and are exposed to the diverse influences of temperature, relative humidity and rate of metabolism.

3. In cases in which no strict control of the dietary of the test meal is attempted.

By reason of these circumstances, early diagnosis, by this method of renal insufficiency, is hazardous unless frequent tests consistently show renal involvement.

Studied as groups, the several classes of kidney nephropathies have presented the various types of pictures described for them by Mosenthal. This last statement we submit as a summary of our findings in over 200 routine test meals to nephritic patients in the medical ward of Roosevelt Hospital.

A STUDY OF PAROXYSMAL TACHYCARDIA, WITH ESPECIAL REFERENCE TO TACHYCARDIA OF VENTRICULAR ORIGIN *

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Since 1913 there have been under observation in the wards of the Peter Bent Brigham Hospital eighteen patients with rapid heart possessing the characteristic features of paroxysmal tachychardia; namely, sudden onset and offset, constant, regular, rapid rate and typical electrocardiographic tracings. These cases present, for the most part, the usual, oft described histories and physical findings. In the majority of cases the pacemaker lies in the auricle, as demonstrated graphically. Of this type there were sixteen cases.

The second type includes such cases as show a ventricular origin of the impulse, during the paroxysms. This occurs surprisingly infrequently. Occasion is therefore taken to summarize briefly the previous similar cases that have found their way into the literature and to add two from our own series.

Reports of cases electrocardiographically showing ventricular tachycardia and similar electric complexes are infrequent. We herewith present a brief summary of descriptions of this and allied conditions.

Hart[1] reports a case of paroxysmal tachycardia, with paroxysms arising from impulses of ventricular origin, from which we quote at some length because of the similarity to one of our cases. The patient had for one year been troubled with palpitation and dyspnea, with some cough and mucous expectoration, but with no edema of the legs. The heart was not enlarged and was essentially negative, except for a soft blowing systolic murmur heard at the apex. The slow, regular rhythm was frequently interrupted by premature beats, followed by pauses, and again by short periods of rhythmic tachycardia at a rate of approximately 200 per minute. The paroxysms lasted from a few seconds to three minutes and gave much precordial distress. The premature beats frequently gave a bigeminal or trigeminal character to the pulse. After leaving the hospital the patient was seen several times, employed in the heaviest kind of labor, and feeling perfectly well. Electrocardiograms during the slow period showed a reduplicated P-wave, increased P-R interval, and a ventricular complex which was prolonged so as to

* Submitted for publication Dec. 6, 1917.
* From the Medical Service of the Peter Bent Brigham Hospital.
1. Hart, T. Stuart: Paroxysmal Tachycardia, Heart, 1912, **4**, 128.

occupy 0.45 second. Diastole lasted 0.33 second. During the paroxysms the curves were identical in character to those of preceding ventricular extrasystoles and indicated also what was taken to be a reversed auricular activity due to the passage of the stimulus from the ventricle to the auricle. During the paroxysms alternation was in evidence. The premature ventricular contractions were sometimes of left-sided apical type, sometimes of right-sided basal type. Hart concluded that his case of paroxysmal tachycardia offered evidence of damage to considerable portions of the myocardium, because of: (1) damaged auricular tissue (abnormal P complex, dropped beat); (2) damaged junctional tissue (lengthening of P-R interval); (3) damaged ventricular tissue (abnormal QRS complex, ventricular beats of two types, periods of tachycardia, composed of ventricular premature beats, alternation).

Lewis[2] reports a paroxysm of tachycardia shown electrocardiographically to be of ventricular origin, which was of approximately five minutes' duration. Experimentally he has produced, by ligation of a coronary artery, and by the administration of poisons such as digitalis, aconitin and muscarin, a sequence of events corresponding quite accurately to those described in the case reported in this paper; namely, ventricular extrasystoles, followed by ventricular tachycardia of short duration. If the experiment, such as ligation of the coronary artery, is continued the ventricular tachycardia increases in rate to 300 or even 450 beats per minute and then goes over imperceptibly into fibrillation of the ventricles.

Lewis[3] also reports a case which over a period of years showed single and successive extrasystoles, indicated by the electrocardiograph to be of ventricular origin. The greatest number of successive ventricular extrasystoles recorded in this patient was eleven. These formed the characteristic regular, rapid rhythm with which we are dealing. Bigeminy and trigeminy were of frequent occurrence. The patient on frequent admissions usually showed moderate symptoms of impaired heart action such as shortness of breath on exertion, precordial uneasiness and palpitation.

Cohn and Fraser[4] report a case of "paroxysmal tachycardia of doubtful, possibly ventricular, origin" in which the paroxysms were controlled by pressure, especially over the left vagus nerve. The paroxysms of tachycardia appear to have been of longer duration than those described by Lewis and by Hart and there was absent the high

2. Lewis, Thomas: Mechanism of the Heart Beat, London, 1911.
3. Lewis, Thomas: Single and Successive Extrasystoles, Lancet, London, 1909, **1**, 382.
4. Cohn, Alfred E., and Fraser, Francis R.: Paroxysmal Tachycardia and the Effect of Stimulation of the Vagus Nerve by Pressure, Heart, 1913, **5**, 93.

incidence of ventricular extrasystoles. Premature ventricular beats were, however, recorded at the onset of some of the periods of tachycardia, but the curves following these single beats showed a different complex, thereby indicating that the pacemaker was not located at the same point in the ventricular muscle as was the site of origin of the preceding extrasystoles.

Lea[5] reports a very interesting case of auricular fibrillation associated with a high degree of auriculoventricular block and with attacks of paroxysmal tachycardia. This case had presented the findings of auricular fibrillation for probably two years previously. Administration of digitalis produced first, partial heart-block, then complete heart-block, and then there ensued, at intervals, paroxysms of rapid, regular rhythm showing by the polygraphic tracings the ventricular type of venous curve. From accurate measurements Lea assumes that the ectopic beats are of ventricular origin. Premature beats between paroxysms were relatively frequent. He suggests that this new rhythm formation may be the result of digitalis action and notes that within a few hours after the discontinuance of digitalis, the attacks disappeared entirely. The highest number of consecutive beats recorded in a single paroxysm was 59, occurring during a period of 29.5 seconds, with a pulse rate of 120. No electrocardiograms were made.

White[6] describes a case of gross cardiac arrhythmia which without graphic study might easily have been mistaken for auricular fibrillation. The condition resulted from an unusual combination of ectopic ventricular contractions, arising from at least three different points in the ventricle, and with an occasional additional extrasystole of supraventricular origin. Bigeminy was frequently present. Only rarely were short runs of normal rhythm to be found. Electrocardiograms showed the presence of defective conduction in the right branch of the atrioventricular bundle.

A case is reported by Hoffmann[7] in which a paroxysm of auricular tachycardia was shown electrocardiographically to terminate with a series of atypical electrical complexes which persisted over a period of two seconds. The onset of these atypical complexes was marked by two ventricular extrasystoles and the subsequent electrical variations corresponded quite remarkably to the curves obtained experimentally on the heart of a dog with ventricular fibrillation. Following the last of these unusual complexes was a pause of approximately four-fifths

5. Lea, E. C.: Auricular Fibrillation with a High Degree of A-V Block, and Paroxysmal Tachycardia, Quart. Jour. Med., 1911-1912, **5,** 388.

6. White, Paul D.: An Unusual Type of Gross Cardiac Arrhythmia, Jour. Am. Med. Assn., 1915, **65,** 1276.

7. Hoffmann, August: Fibrillation of the Ventricles at the End of an Attack of Paroxysmal Tachycardia in Man, Heart, 1911, **3,** 213.

second and then the heart took up a normal slow rhythm with occasional ventricular extrasystoles. The events during these two seconds may have been due to successive ventricular extrasystoles arising in various portions of the ventricular musculature, but Hoffmann concludes that they were the result of ventricular fibrillation, his conclusion being based on the similarity to experimental curves obtained in the dog and on the fact that palpation over the carotid artery during this period showed complete absence of the pulse beat.

Out of a series of four cases studied by Butterfield and Hunt[8] one is described in which the electric curves showed the presence of an undoubted ventricular origin. The case was of a man who for some time had been suffering from auricular fibrillation, and with failing compensation the heart rate had risen to the neighborhood of 120. One day it suddenly rose to 150 and became quite regular. This paroxysm lasted throughout four days. Later, ventricular extrasystoles were frequent, and in all three leads the complexes of these extrasystoles correspond accurately to those of the paroxysm.

Two cases of the type not having the customary supraventricular origin of the tachycardia have occurred at the Peter Bent Brigham Hospital and are reported here.

REPORT OF CASES

CASE 1.—*A case of paroxysmal tachycardia showing impulses of auricular origin and, later, of ventricular origin.*

History.—A. H. (P. B. B. H. Med. No. 5742), aged 21, was admitted to the wards Dec. 9, 1916, complaining of "pain and palpitation of the heart." His previous occupations had usually kept him indoors and had never been heavy work. He denied history of alcohol, drugs, tobacco or venereal disease. He drank no tea and but two cups of coffee daily. Past history was negative with the exception of sore throat about twice each year and an attack of "rheumatism" in 1913, with which he was in bed from March 5 until July. From his account it seems probable that the so-called rheumatism was not rheumatic fever. He suffered cardiac pain for the first time in 1914. There were no other cardiac symptoms until a year before admission, when he had his first attack of palpitation. He was a heavy eater and had occasional attacks of "dry heaves" which at times started his heart into "palpitation."

Present Illness.—The present illness is as follows: Palpitation on exertion first occurred one year previous to admission. He had then dyspnea and no pain. In the first half year he had only three or four of these attacks of presumably auricular tachycardia, but later he developed them as often as three or four times in a week. As he described a typical paroxysm, the heart would beat about 200 per minute, things would get misty, he would become dizzy, sometimes nauseated, and with sudden cessation of palpitation he would feel all right again. About two weeks before admission to the hospital the patient developed two unusually severe attacks, one of which lasted three hours and the second over twenty-four hours. He was in Chicago at the time and as he boarded the train to return to Boston another attack started which lasted until he reached Boston. He describes the trip as "terrible." On arrival the attack was stopped by pressure

8. Butterfield, H. G., and Hunt, G. H.: Observations on Paroxysmal Tachycardia, Quart. Jour. Med., 1913, **7**, 208.

on the eye. This was one week before admission. He had additional attacks of shorter duration during the interval, but they had changed markedly in character from those previously described. He describes a typical attack now as follows: The heart is thumping slowly, then comes one strong beat followed by a long pause and three or four short, small beats in rapid succession. Then one or two strong beats again, which cause violent, painful throbs in his head. This is repeated several times, then quite a pause comes, followed by one very painful hard thump, and next the heart runs away into a rapid succession of weaker, small beats, frequently up to 200 per minute and quite regular. All of this is accompanied by some nausea, somewhat of a cough and marked precordial pain; the patient feels faint and occasionally vomits. With these large pulsations frequently what he looks at seems to pulsate.

Physical Examination.—The physical examination revealed a well developed and nourished individual lying propped up in bed, anxious and apprehensive, apparently very much discouraged. Tonsils were markedly hypertrophied, but not inflamed. There was moderate postnasal catarrh. Lungs and abdomen were normal. Liver dulness extended from the fifth rib to just below the costal margin, where a smooth, pulsating edge was felt. Examination of the heart shows a diffuse, heaving impulse over the apex, of maximum intensity in the fifth interspace, 11 cm. to the left of the midline. The left border of cardiac dulness measured in the sixth space, 14 cm. from the midsternal line. Retromanubrial dulness measures 7 cm. from side to side. The right border of cardiac dulness measured 2 cm. from the midline. No thrills were felt. On auscultation there was a slow, fundamental rhythm frequently disturbed by extrasystoles, with compensatory pauses, many of the beats being stronger than the others, and occasionally going into periods of tachycardia with a rate of about 150 to the minute and quite regular. Pressure on the eyeballs or on the supra-orbital ridge of either eye, when very marked, and occasionally vagopressure, would cause the tachycardia to cease, with a resulting slow rhythm. (This slow rhythm would not persist long and during the night of admission the patient was having attacks of palpitation for a time as often as once every five minutes.) When the heart was beating slowly, at the apex the first sound was replaced by a systolic murmur which was transmitted both into the axilla and into the back. The second sound was followed by a diastolic murmur. In the tricuspid area there was a less loud systolic and a diastolic murmur. This was blowing in quality. In the aortic region the second sound was nearly replaced by a murmur. Here also there was a to-and-fro blowing murmur. In the pulmonic region there was a more distant to-and-fro murmur. P_2 was moderately sharp. In the fourth left intercostal space a to-and-fro murmur with the second murmur low pitched and blowing was heard. The first sound was not heard. With the heart beating rapidly, at the apex there was only a systolic murmur. The first sound was sharp. The second sound was absent. In the fourth intercostal space both sounds, then, were heard and there was a systolic and a diastolic murmur. The radial pulses were Corrigan in type. The rate varied in attacks from 92 to 180, although the patient said that it had been up as high as 200. The vessels were not markedly sclerosed. Over the femoral arteries there was a pistol shot sound and a Durozier sign. Pressure over the femorals caused a lancinating pain, with occasional huge beats complained of. A murmur was heard in the subclavian artery as a loud rumble close to the ear. A marked systolic pulsation, not well sustained, was seen in the carotids and even up as far as the temporal arteries.

Diagnosis.—Chronic cardiac valvular disease, aortic insufficiency and mitral insufficiency, hypertrophy of the heart and paroxysmal tachycardia.

Treatment.—Soon after admission the patient received 0.015 gm. of morphin sulphate which had to be repeated at the end of an hour. Powdered digitalis leaves was started in doses of 0.1 gm. every three hours.

Course.—Throughout the first thirty-six hours in the hospital the patient had a miserable time, his heart rhythm changing at frequent intervals from a slow regular rhythm through transitions of extrasystoles, in which bigeminy and

trigeminy predominated, to the rapid regular rhythm of the tachycardia. It was during these transitions with the extrasystoles that the greatest distress was experienced, the patient complaining of the terrible thumping in his head. This was probably a result of the aortic insufficiency and the consequent large pulse pressure present. During the tachycardia, which at times went as high as 180 beats per minute, the distress was mostly precordial. From the time of admission pulsus alternans was noted.

Thirty-six hours after admission, at 7:00 a. m. and after a restless night, the patient passed into a curious state of unconsciousness from which he could not be aroused, and during which respiration was periodic in type, with forceful attempts at expiration, during which he would throw his head back and would jerk it convulsively, but without true convulsions, this alternating with long periods of apnea. The pupils were normal in size and reaction. The heart rate was 124 to the minute, quite regular, with no pulse deficiency, the pulse being of good quality. The attack lasted fifteen or twenty minutes, after which respiration again became regular and consciousness returned.

Throughout the day the patient felt much improved and the paroxysms of tachycardia became much less frequent, but there was an increase in the frequency of extrasystoles in which there occurred at times short runs of ectopic beats at a rapid rate, similar clinically to the rhythm in the preceding tachycardia. These new, regular, rapid rhythms, however, yielded neither to vagopressure nor to ocular pressure. As will be shown later, they were a result of new impulse formation occurring in the ventricles. Digitalis was discontinued on this day after the patient had received in all 1.4 gm. of the powdered leaves.

During the following night he developed a second period of syncope which lasted nearly two hours and was similar in character to the first. Electrocardiograms at this time showed no further new rhythm. From this time the patient's condition improved both subjectively and objectively, the extrasystoles becoming less and less frequent, and finally disappearing. During the last two weeks in the hospital the heart rate and rhythm remained absolutely normal with the exception of a moderate sinus arrhythmia. The patient remained in the hospital in all twenty-six days, during the last eleven of which he was up and about, exercising quite freely and without return of symptoms. The pulse remained constantly below 90 per minute.

Roentgenograms taken during a paroxysm of tachycardia showed the transverse diameter of the heart to be 16.5 cm. as contrasted with a transverse diameter of 15.5 cm. taken when the heart rate was normal. At no time during the course of the disease were there any signs of venous stasis. Ten months after his discharge from the hospital, the patient was reported to be in good condition and doing relatively hard manual labor in a theater. He has had no recurrence of paroxysms.

Electrocardiograms.—The accompanying curves, taken by Dr. W. S. Wells, are reported through the kindness of Prof. Henry A. Christian.

Figure 1 shows the three leads taken during the first twenty-four hours in the hospital and in it can be seen the auricular form of paroxysmal tachycardia. P-waves are inverted and occur in the T-waves. T-waves appear inverted also. The heart rate is 160 to the minute. There is no evidence in these curves of left ventricular hypertrophy. It will be remembered that the transverse diameter of the heart was 16 cm. and that the patient was suffering from an aortic lesion. The tracings in black below the electrocardiographic curves present a pulse tracing taken with the Erlanger apparatus and Frank capsule. They show the typical collapsing pulse of aortic insufficiency, and in

addition show that alternation of the pulse was present on admission. Pulsus alternans is usually present with such rapid rates and is not of prognostic importance.

In Figure 2 a, pressure on the right eye over a period of eight seconds caused a change from a rate of 150 beats per minute through temporary sino-auricular block, then two normal beats, and finally one

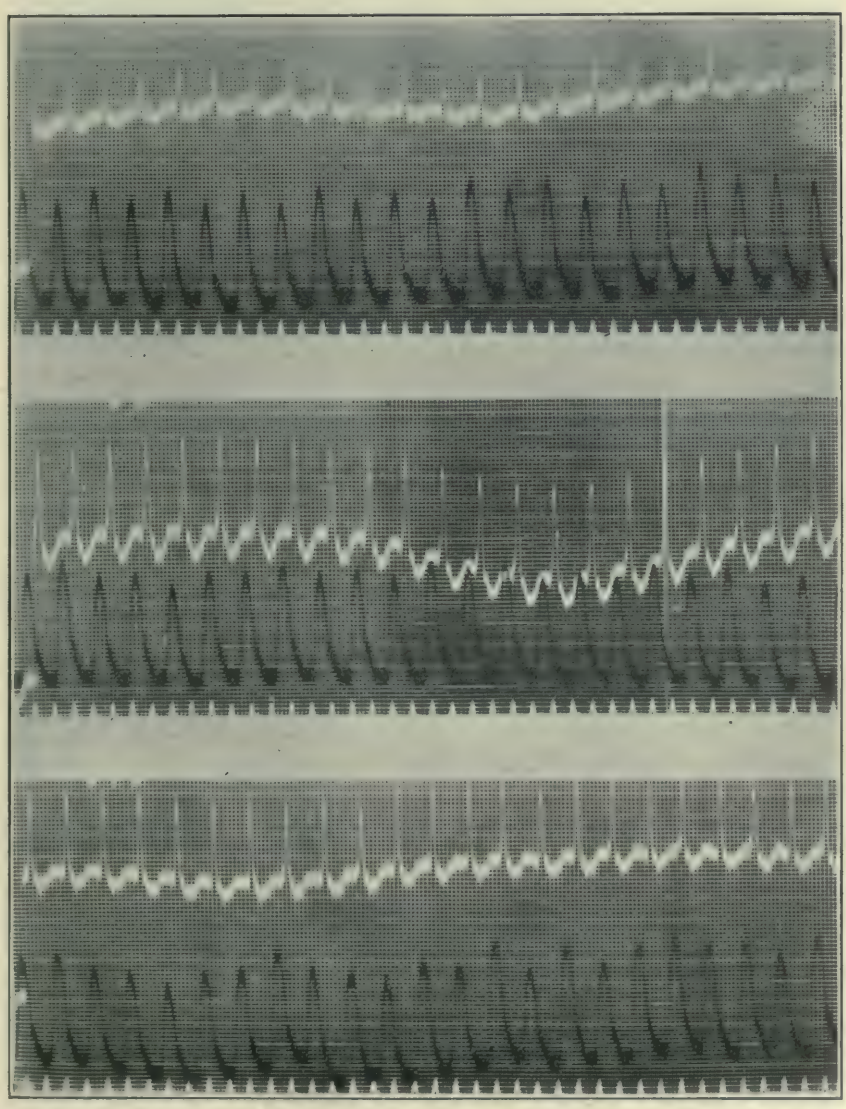

Fig. 1.—A. H., Dec. 9, 1916, 2:30 p. m. The ventricular rate is 162. Inverted P-waves occur in the T-waves. The P-R time is about $\frac{6}{25}$ second. The tracing in black is a pulse record taken with an Erlanger apparatus and Frank capsule. Diagnosis: auricular tachycardia; pulsus alternans.

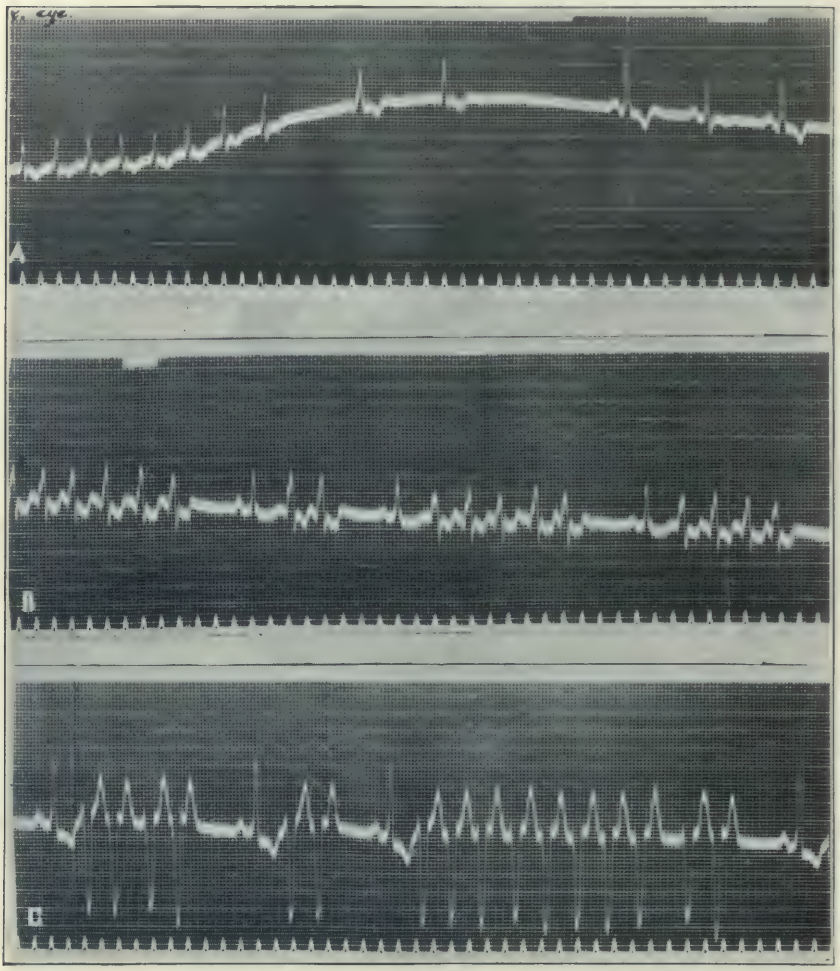

Fig. 2.—A. H. (*a*), Dec. 9, 1916. The tracing shows that pressure on the right eye causes delayed conduction, S-A heart-block, A-V heart-block and then the heart picks up a normal rhythm with upright P-waves. Pressure on the right and left vagus nerves was without effect. At another time pressure on the left eye also caused a change from auricular tachycardia to normal, as shown by the electrocardiogram. In both instances the heart was again in tachycardia within five minutes.

(*b*) and (*c*), Leads 1 and 2, Dec. 11, 1916, 10:10 p. m. A majority of the beats are extrasystoles arising in the left ventricle. These occur in series of two to sixteen beats. The P-waves cannot be made out in the ectopic complexes. These tracings were taken during an attack of syncope and are, essentially, the same as those taken before and after the syncopal attack. Lead 3 (not shown) shows the same type of curve as Lead 2, but with a deeper downward stroke.

Diagnosis: paroxysmal ventricular tachycardia.

of auriculo ventricular block, to a normal rhythm with an upright P-wave and an inverted T. The P-R interval is here four twenty-fifths of a second. After the first ten normal beats the heart increased slightly, to 110 per minute. Subsequently there occurred premature ventricular beats producing bigeminy and trigeminy, and within a few minutes the heart was again in auricular tachycardia (not shown on the curve). The curves of Figure 2 a were taken ten minutes after those in Figure 1. Twenty minutes later the same change from auricular tachycardia to normal rate was produced by pressure on the right vagus. After normal rate persisted for a short time ventricular extrasystoles became frequent as before and in a few minutes more auricular tachycardia was reestablished. Pressure on the left vagus caused no change in the auricular tachycardia.

In Figure 2 b and c, taken two days later, are seen numerous ventricular extrasystoles, occurring sometimes in pairs or short runs, and interpolated with normal beats. The normal P-waves preceding the beats of supraventricular origin are, as in the last curve, upright and tend to be doubled. Following the extrasystoles are pauses of about the length of diastole when the heart is at normal rate. The longest period of ventricular tachycardia recorded on the tracings is of ten beats' duration. Vagopressure and oculopressure while the heart was in this condition were without effect. The P-R interval measures five twenty-fifths second. The patient had received up to this time while in the hospital 1.4 gm. of digitalis leaves. How much he had taken before admission is uncertain, but it was probably a small amount. The curves of Figure 2 b and c were taken during a syncopal attack described above, but were similar in every respect to those taken before and after the attack.

Figure 3, taken eighteen hours after Figure 2 B and C, shows a predominance of the normal rhythm with a P-R interval of five twenty-fifths second and much less numerous, though still very frequent, ventricular extrasystoles producing in Lead 1 a bigeminy. Pauses are fully compensatory. P-waves as a rule show but one crest. T-waves in all three leads are inverted. The heart rate is about 95 per minute.

Three weeks after the last tracings described and three weeks after digitalis had been omitted, the tracings of Figure 4 were taken, which show normal complexes with the exception of inverted T-waves in all three leads. P-waves are all upright and the P-R interval measures five twenty-fifths second. The heart rate is 73 per minute. Heart sounds from the base of the heart are recorded by phonocardiogram and show a continuous vibration due to to-and-fro murmur. Pulse tracings in Lead 3 fail to show definite evidences of alternation. This is especially interesting when compared with the pulse tracings of Figure 1.

This case shows in addition to evidence of severe cardiac damage by valvular disease, attacks of auricular tachycardia and later of ventricular tachycardia.

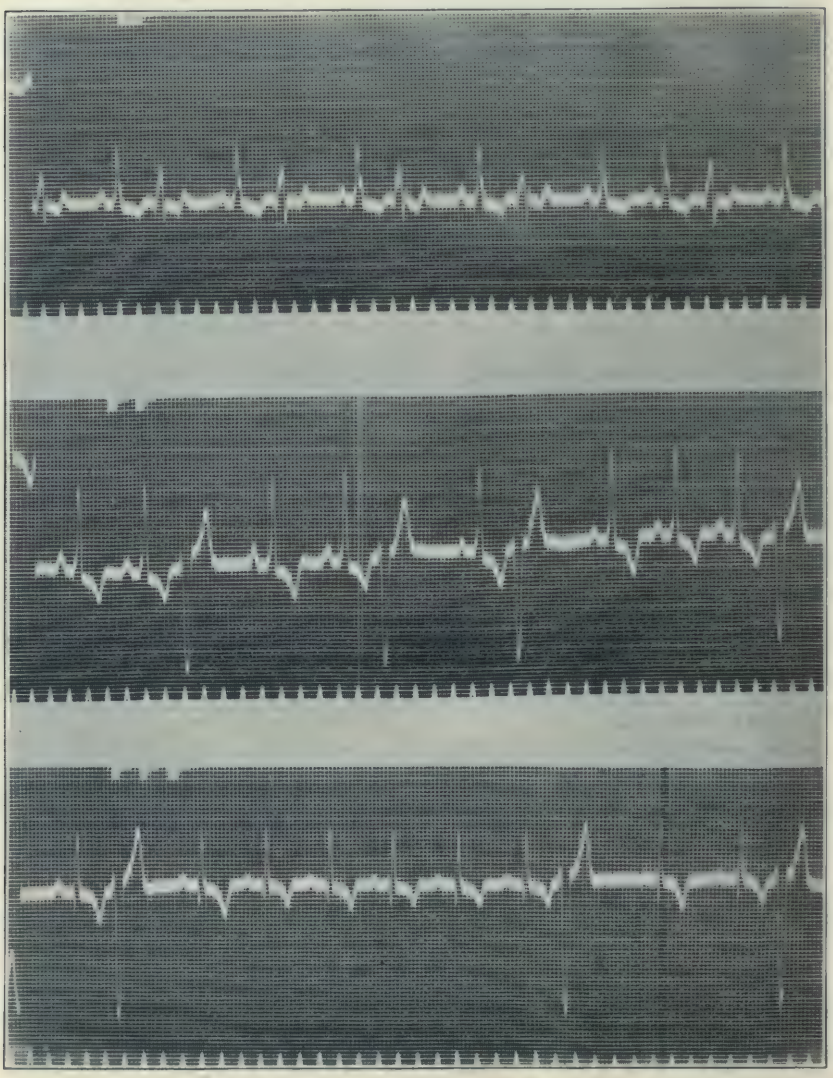

Fig. 3.—A. H., Dec. 12, 1916, 4 p. m. No runs of premature beats occur, as yesterday, but the extrasystoles are very numerous. The T-waves are greatly depressed. Diagnosis: premature ventricular beats.

There is evidence in this case, as in other cases quoted, of severe and widespread myocardial damage. This is seen in the paroxysms of auricular tachycardia, the reduplication of the P-waves, the inverted

T-waves, the ventricular extrasystoles, the premature nodal beat, and, finally, the presence of definite valvular lesions. In contrast to the curves obtained by Hart, all of the ectopic ventricular beats show the point of origin to be the same, apparently, in the left or apical portion of the ventricles, and there is no evidence of beats arising from the

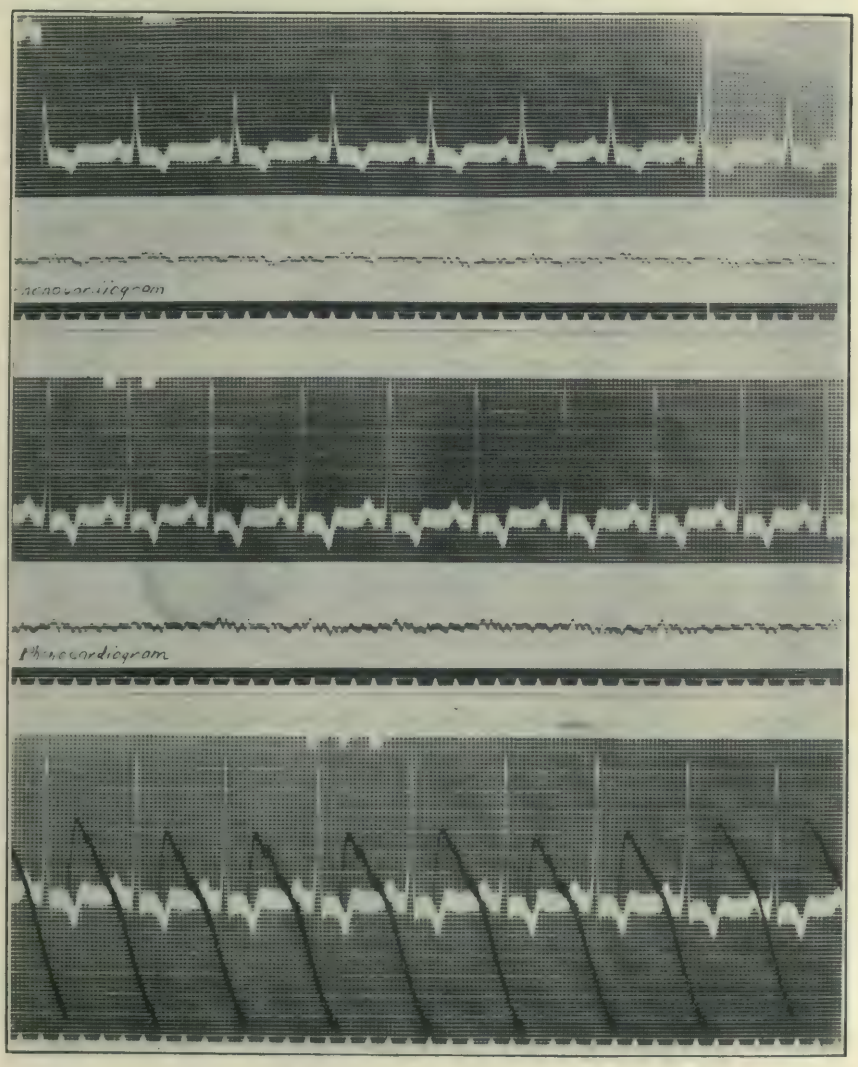

Fig. 4.—A. H., Jan. 3, 1917. In Leads 1 and 2 are records of the heart sounds at the base of the heart. There is a continuous vibration due to a to-and-fro murmur. Lead 3 shows a simultaneous pulse tracing. The T-waves are inverted in all leads and the P-waves are upright. The P-R interval is $\frac{5}{25}$ second. The R-waves are large in Leads 2 and 3. In previous curves occasional premature nodal and premature auricular beats have been recorded.

right or basal portion. All of the ventricular ectopic beats show a similarity, not only in the curves here produced, but also in other numerous curves taken.

As regards etiology, digitalis may not be lightly ruled out. It cannot be definitely proved with the evidence at hand that the cessation of symptoms within twenty-four hours after the discontinuance of digitalis in two somewhat similar cases (this case and that reported by Lea) is but a coincidence. But the amount of digitalis used in our case was near the lower limits necessary for physiologic effect. If digitalis is a factor, there must be an additional, and probably more important "predisposing" factor as contrasted to the former, which might be termed "exciting." This predisposing factor is in all probability a hyperexcitability of the damaged musculature. In the case here reported the former effect is very slight, as evidenced by a normal P-R interval, whereas the latter is the dominant feature. The incidence of aortic valvular disease in this case may be conceived to have some etiologic connection with the paroxysms of ventricular tachycardia when we consider that in such hearts the coronary arteries are frequently damaged and that Lewis[2] is able to produce experimentally ventricular extrasystoles and tachycardia by ligation of the coronary artery. The possibility of this being a factor is further emphasized by the fact that the ventricular ectopic beats arise from but one portion of the ventricle.

The attacks of syncope remain unexplained, but probably were greatly influenced by the condition of the peripheral circulation, the rapid and irregular beats being inefficient in pumping sufficient nourishment to the cerebral centers.

CASE 2.—*A case of paroxysmal tachycardia in which the site of impulse formation may be in the ventricle.*

History.—F. N. (P. B. B. H. Med. No. 5503), aged 50, was admitted to the wards Oct. 25, 1916, and discharged improved, Nov. 16, 1916. The patient's past history was essentially negative, except that he had used much alcohol during his life. Twenty years previously he had had "malaria" for six weeks. Also he had had a mild attack of gonorrhea when he was 19 years old. One year before admission he had had an attack of indigestion with belching of gas two or three hours after meals and occasional vomiting of greenish material, which condition persisted for ten days. Six weeks before admission he had a similar attack, which was accompanied by severe palpitation and a noticeably rapid heart. Paroxysms of palpitation came at frequent intervals since and with increasing severity, usually lasting about fifteen minutes at a time and occurring every day during the previous three weeks. Dyspnea and orthopnea had been very great, but there was no history of precordial or abdominal pain and no edema was present.

Physical Examination and Course.—On examination the heart was found to be slightly enlarged to the left and with a rapid, regular rate (from 150 to 180 per minute) which did not respond to vagus stimulation. There was no pulse deficit. The liver was enlarged and tender. The lungs were emphysematous throughout. Systolic blood pressure was 98 mm., diastolic 80 mm.

The exact duration of the attack from which the patient was suffering at admission was uncertain, but it persisted throughout three days in the hospital. Cessation was sudden and followed by a heart rate of 100 per minute. With the heart beating slowly, a soft, blowing systolic murmur became audible in the apex region. During the tachycardia various remedies were prescribed, including vagopressure, and morphin which was given to relieve the patient's distress. One c.c. of digipuratum was given intramuscularly and this was followed by a course of digitalis. During the paroxysm the patient's subjective condition became so grave that he was placed on the danger list. Four days after the paroxysm had ceased the patient became extremely uncomfortable and com-

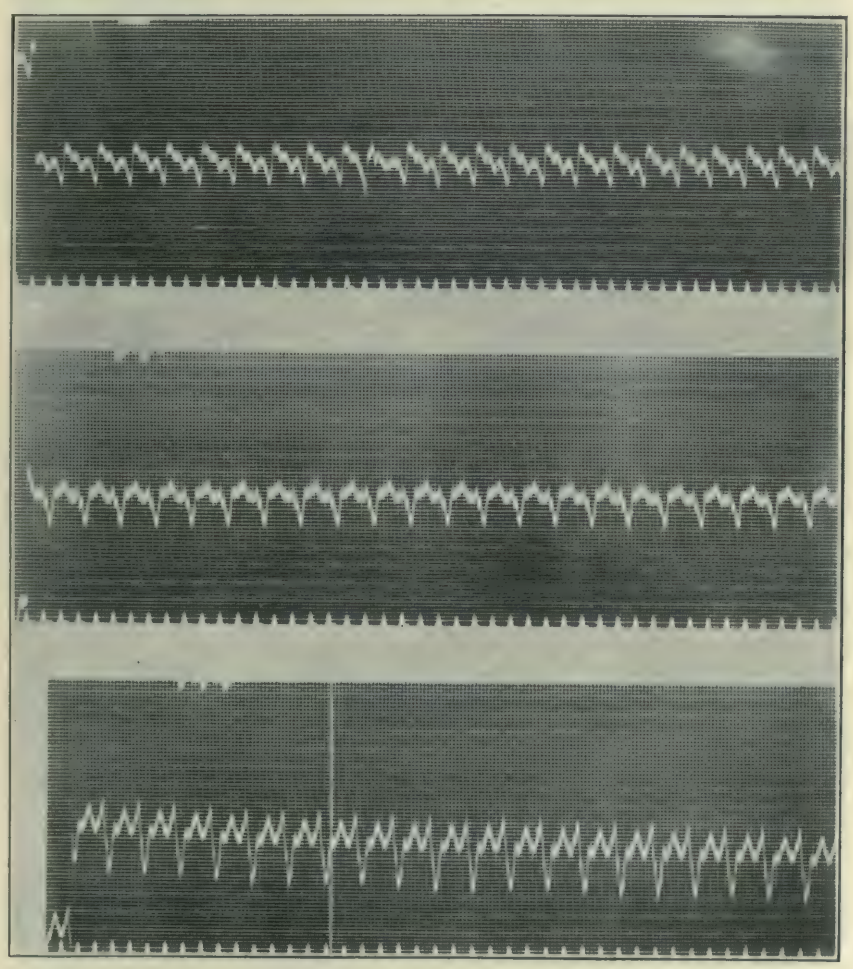

Fig. 5.—F. N., Oct. 26, 1916, 9:30 a. m. This is an unusual type of tachycardia. No P-waves can be made out. In Leads 2 and 3, the ventricular complexes look like those which might arise in the left ventricle, but in Lead 1 they are atypical. Rate 150. In this curve occasional complexes come prematurely and are followed by a notch. In other curves such premature complexes are not seen. Pressure on the vagi and eye had no effect except slowing the heart. Elevating the foot of the bed thirty inches had no effect. Diagnosis: paroxysmal ventricular tachycardia.

plained of palpitation. The heart at that time was beating around 160 per minute with every third or fourth beat a ventricular extrasystole, the premature beats not being felt at the wrist. Bigeminy was also present at times. This paroxysm of tachycardia with irregular rhythm lasted for three or four days, with occasional intervals of normal rhythm. After this he had no recurrence and rapidly improved until the time of discharge.

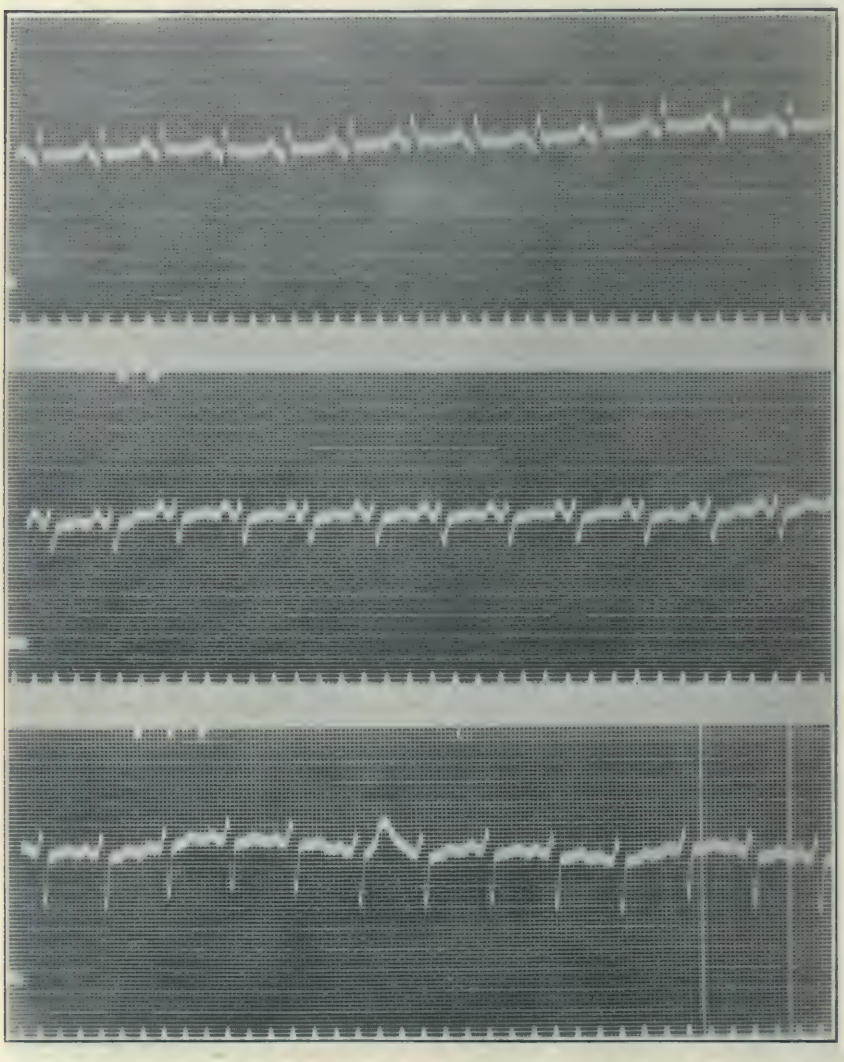

Fig. 6.—F. N., Oct. 28, 1916, 9:30 a. m. The heart now has a normal rhythm with a rate of 100. Large P-waves are present. The ventricular complexes have greatly changed but still suggest some bundle effect. Diagnosis: left ventricular hypertrophy? or defective conduction of the right branch of the bundle of His?

Electrocardiograms.—The electrocardiographic tracings (Fig. 5) taken during a paroxysm and soon after admission to the hospital

show an unusual type of complex, not at all characteristic of paroxysmal auricular tachycardia. No P-waves could be made out. In Leads 2 and 3 the QRS interval is prolonged, as would be the case in ventricular extrasystoles or in right bundle block. A rather high upward deflection beginning five-tenth second before the R-wave in

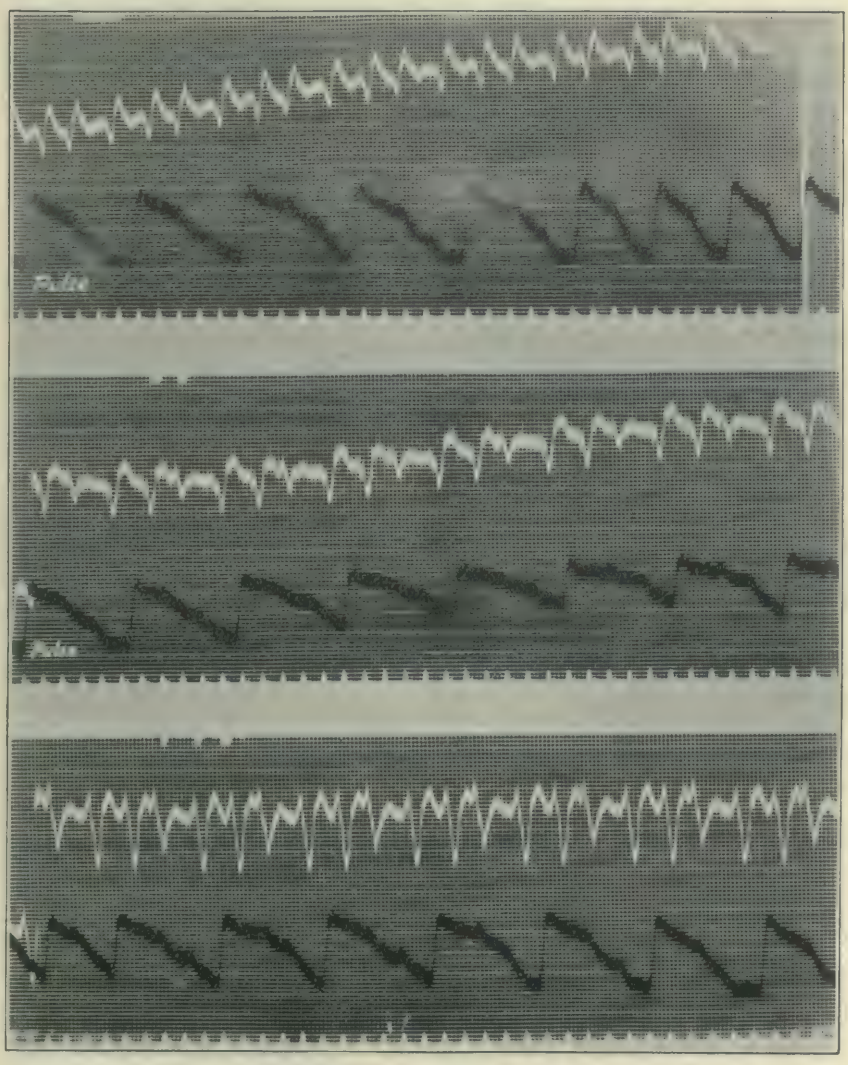

Fig. 7.—F. N., Nov. 3, 1916, 11 a. m. The heart is again in tachycardia with every second or third beat occurring prematurely. The rate is 167. The P-waves cannot be made out. Vagal stimulation has no effect on the rhythm. Note the variation in the pulse with variation of the rhythm. Soon after this tracing was taken the heart became regular at the same rate (167). The pulse tracing changed so that every beat was of constant size.

all three leads may be simply a T-wave or it may be a T-wave with a superimposed P-wave. In the downward deflection of the R-wave in Lead 2 is found a constant slight electrical variation which might also indicate a P-wave. This can also be made out indistinctly in Lead 1, but it is not found in Lead 3. Comparison of Figure 5 with Figure 6 taken after the heart has resumed its normal rhythm shows that especially in Leads 2 and 3 the QRS complex still has some similarity to that of the rapid rhythm. There is some suggestion of bundle defect, but the deflection in the downward stroke of the R-wave is now absent. The P-R interval is here four-twenty-fifths second. If, then, the P-waves in Figure 5 precede the R-waves by about five

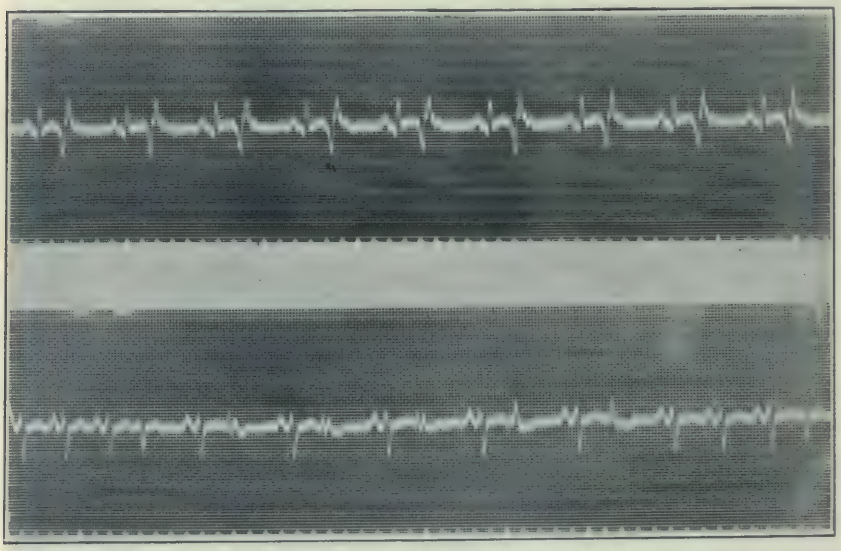

Fig. 8.—F. N., Nov. 5, 1915, 10:30 a. m. There are many premature ventricular beats, and complexes similar to those in the tachycardia can be found. One cannot with certainty locate P-waves occuring during the extrasystoles. Diagnosis: left ventricular hypertrophy; premature ventricular beats.

twenty-fifths second they will be seen on the curve to coincide with the T-waves in Leads 2 and 3. In Lead 1 the position of the P-wave is more obscure.

With the heart again in tachycardia and with every third beat coming prematurely as is shown in Figure 7, we are dealing with ectopic beats from two distinct sources — the first being identical with that found in Figure 5, the second being in the left or apical portion of the ventricle. In these curves there is seen rather a suggestive similarity between the two types of ectopic complexes, which strengthens but far from confirms the suspicion that both types are of ventricular origin. The curves of Figure 8, taken after the second

paroxysm had ceased, show in Leads 1 and 2 and also in Lead 3 (not reproduced) evidence of left cardiac hypertrophy. They also show curves of premature ventricular beats arising from at least two foci, neither of which is identical with the possible focus discussed in Figure 5. Later, electrocardiograms all show a nearly normal electrocardiographic complex.

It is impossible to determine definitely whether this patient has had an attack of paroxysmal auricular tachycardia in which there was present at the same time left ventricular hypertrophy and defective conduction in the His bundle, or whether he had an attack of true paroxysmal ventricular tachycardia. The evidence, I believe, favors the first possibility.

DISCUSSION

In the cases studied we have one instance of undoubted paroxysmal ventricular tachycardia and one in which the site of impulse formation cannot be definitely located, but may be in the ventricle and is again of the paroxysmal tachycardia type. The interesting feature is that of eighteen cases of true paroxysmal tachycardia only two show electrocardiograms similar in character to those shown experimentally to be due to impulse formation within the ventricular walls. All of the others are of auricular origin. Isolated ventricular extrasystoles, supposed to be the result of a hyperirritable condition of an isolated portion of ventricular musculature, are clinically of frequent occurrence, being perhaps the most frequent cardiac arrhythmia recorded graphically outside of sinus arrhythmia. Moreover, in view of the frequency of administration of digitalis in various chronic conditions, and in consideration of the well known action of the drug in increasing the muscular irritability, it seems contrary to expectation that runs of ventricular extrasystoles should be so rare.

Considering this, we have reviewed 189 cases in the records of the medical service of the Peter Bent Brigham Hospital, among the diagnoses of which there was present in each case that of premature ventricular beats. The majority of these cases showed additional cardiac disease and 118, or 63 per cent., received therapeutic doses of digitalis while in the hospital. Of the 189 cases, but seven, or 4 per cent., showed two successive ventricular extrasystoles, among which one showed three in succession. (This case was included in a series reported by Christian.[9]) Two of the patients with duplicated extrasystoles received no digitalis, but one of these had severe cardiac damage and showed also bigeminy. He died within two days after

9. Christian, Henry A.: Transient Auriculoventricular Dissociation, with Varying Ventricular Complexes Caused by Digitalis, THE ARCHIVES INT. MED., 1915, **16**, 341.

admission. All the other cases received some digitalis preparation. Twenty-three cases, or 12 per cent., showed bigeminy by the electrocardiogram. Four of these received no digitalis. In a large proportion of these 189 cases digitalis was not administered until after the curves had been made, because the custom has been to take tracings in cardiac patients showing nothing very unusual, soon after admission, and to repeat only if there is some change. But on subsequent tracings, when made, no increase in the number of successive extrasystoles appears. Where subsequent tracings were not made there was no intimation of such a condition in the clinical notes. It is safe to say that had such a condition occurred, it would have aroused suspicion and further electrocardiograms would have been made. We may conclude, therefore, that digitalis in therapeutic doses in the majority of cases does not markedly increase the tendency to successive ventricular extrasystoles.

The next question is, naturally, as to the effect of toxic doses of digitalis. Of twenty cases having among their diagnoses the electrocardiographic diagnosis of digitalis intoxication, but two had two successive ventricular extrasystoles, and one more (previously referred to) had three in succession. Bigeminy was rather frequent, trigeminy less so, but the most usual indication of digitalis intoxication was interference, to varying extent, with conduction from the auricles to the ventricles. Auricular flutter and fibrillation were also noted in a case with digitalis intoxication, but occurring in a moribund heart.

SUMMARY

In eighteen cases of paroxysmal tachycardia only two, which are here reported in detail, showed a site of impulse formation elsewhere than in the auricles. Study of the literature points to the infrequency of cases of paroxysmal tachycardia of ventricular origin. To those already reported two are added. Digitalis may be an exciting cause in the production of the condition, but there must be some other predisposing factor such as ventricular hyperirritability from impaired blood supply or from some other cause.

PHARMACODYNAMIC EXAMINATION OF THE VEGETATIVE NERVOUS SYSTEM IN TYPHOID FEVER

A CONTRIBUTION TO THE PROBLEM OF BRADYCARDIA *

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The hypothesis of vagotonia and sympathicotonia, established by Eppinger and Hess,[1] gave a clearer explanation of diseases whose pathology was heretofore not quite obvious, thereby opening a new way to diagnosis and treatment.

According to their orginal opinion, there exists an equilibrium between the sympathetic and autonomic (parasympathetic) nervous systems, through which the inner organs and the involuntary apparatus perform their functions smoothly. When this equilibrium is once disturbed, however, from any cause, the action of one becomes predominant, and various pathologic conditions arise. By means of drugs which act especially on the vegetative nervous system, this disturbance becomes so marked that it greatly facilitates the diagnosis.

This disturbance is due to the abnormal tonus of either the sympathetic or autonomic nervous system; in other words, everybody who is sensitive to atropin and pilocarpin is not sensitive to epinephrin, and vice versa. They named the former condition vagotonia, the latter sympathicotonia. They did not observe any one who was sensitive to both groups (atropin-pilocarpin and epinephrin), at least in the doses they used.

Later it became necessary to make some corrections, as their original opinion seemed to be too dogmatic, for there were some individuals who were sensitive to all three drugs.

Even Eppinger and Hess themselves, together with Pötzl,[2] observed such a condition in some psychoses. Falta, Neuburgh and Nobel[3] observed some persons who were sensitive to both epinephrin and pilocarpin.

Since this hypothesis was established, many investigators have tested the functions of the vegetative nervous system in their clinics and published their results. Petrén and Thorling,[4] in their observa-

* Submitted for publication Dec. 20, 1917.

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1. Eppinger and Hess: Ztschr. f. klin. Med., 1909, **67,** 345; *ibid.,* 1909, **68,** 205; *ibid.,* 1909, **68,** 231.
2. Pötzl, Eppinger and Hess: Wien. klin. Wchnschr., 1910, p. 1381.
3. Falta, Neuburgh and Nobel: Ztschr. f. klin. Med., 1911, **72,** 97.
4. Petrén and Thorling: Ztschr. f. klin. Med., 1911, **73,** 27.

tions on ulcer of the stomach, found numerous cases of vagotonia, but very few of sympathicotonia. This coincided with what Eppinger and Hess had reported. At the same time, however, they could not deny the existence of individuals who were sensitive to epinephrin and pilocarpin; so they concluded that a man who is sensitive to atropin and pilocarpin is not entirely nonsensitive to epinephrin, and that atropin and pilocarpin do not always act in parallel. They emphasized the difference between the elevation of tonus and that of irritability. When the tonus is elevated, it must be sensitive to both kinds of drugs, the paralyzing and the stimulating. Bauer[5] examined many patients who were considered by Eppinger and Hess to be vagotonic and sympathicotonic, and found that many of them were sensitive to both epinephrin and pilocarpin. In cases which were supposed to be of sympathicotonia, he found strong reaction for pilocarpin. Lehmann[6] examined 100 persons, including a variety of patients and some healthy controls, and found that 95 per cent. of those sensitive to epinephrin were also sensitive to pilocarpin. On the other hand, pilocarpin and atropin did not act in parallel. Thus they both doubted the hypothesis of Eppinger and Hess.

Besides these, Deutsch and Hoffmann[7] utilized this test in pulmonary tuberculosis; Wentges,[8] Ando,[9] as well as Hopkins,[10] in functional nervous diseases; Thies[11] in diseases of the bile duct.

Molchanoff and Lebedeff[12] tried this test in ten children with scarlet fever, during the period of recovery, and recorded the majority of these cases as of distinct vagotonia.

No one has as yet, however, undertaken such a test on typhoid fever. This fact alone awakes some interest. In typhoid fever, as is well known, there sometimes exists striking bradycardia, even in the fever period, for which there is no satisfactory explanation. Our work is an attempt at a solution of this problem through the hypothesis of Eppinger and Hess. Our investigation, in fact, started with this point in view.

Material for Experiments.—As material we used typhoid fever patients, including seven cases of paratyphoid B, who were admitted to the Kyoto Infectious Disease Hospital, all bacteriologically and serologically proved. Up to the time of examination no complication

5. Bauer: Deutsch. Arch. f. klin. Med., 1912, **107,** 39.
6. Lehmann: Ztschr. f. klin. Med., 1914, **81,** 52.
7. Deutsch and Hoffmann: Wien. klin. Wchnschr., 1913, p. 569.
8. Wentges: Deutsch. Arch. f. klin. Med., 1914, **113,** 607.
9. Ando: Kyoto Igaku Zassi., 1916, **13,** No. 1.
10. Hopkins: The Archives Int. Med., 1913, **22,** 556.
11. Thies: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1914, **27,** 389.
12. Molchanoff and Lebedeff: Russk. Vrach., cited in Jour. Am. Med. Assn., 1916, **67,** 475.

had set in. All were more than 14 years old. We avoided patients who were in excited states. At first we chose patients who had relative bradycardia, as they were the most suitable for our purpose. Afterwards, however, we also tested as controls patients who had no bradycardia, and some with tachycardia.

Method of Experiment.—For the pharmacodynamic examination we used atropin, pilocarpin and epinephrin. It is necessary to make a few remarks concerning the doses used. Eppinger and Hess administered hypodermically atropin, 0.001 gm., to men, 0.00075 to women; epinephrin 0.001 gm. for men, 0.00075 for women; and pilocarpin 0.01 gm. for men, 0.0075 for women. Three hours before the injection of epinephrin 100 gm. of glucose were given per os. Petrén and Thorling used almost the same doses as Eppinger and Hess. Bauer gave relatively small doses, namely, pilocarpin 0.007 gm., epinephrin 0.0007, giving 100 gm. of glucose three hours before the injection, and of atropin 0.0005 gm. Wentges used the same as Bauer. Lehmann almost the same as Eppinger and Hess.

To criticize such a new hypothesis it is best to follow the original method; therefore we adopted the doses of Eppinger and Hess: atropin 0.001 gm., epinephrin 0.001 gm., subcutaneously. According to Burgusch and Schittenhelm,[13] in cases in which 0.001 epinephrin was injected following 100 gm. of glucose per os, glucose could be found even in the urine of the healthy. So we tested glycosuria qualitatively without giving glucose previously. As intestinal hemorrhages may take place by increased peristalsis, we used 0.007 gm. pilocarpin instead of 0.01 gm. (Eppinger and Hess).

After injection of atropin, rate of pulse, degree of thirst and palpitation were observed for from one to one and one-half hours. After injection of epinephrin, pulse, blood pressure (by Riva-Rocci), body temperature (axillary), respiration, tremor, palpitation and pallor were observed for one hour, and glycosuria was tested for (Trommer and Nylander). After injection of pilocarpin, pulse, salivation, sweating and gastro-intestinal disturbances were observed for one hour.

Besides the pharmacodynamic test, respiratory arrhythmia, Aschner's bulbus phenomenon and dermographia were observed, but Tschermack's press trial was not tested.

All patients in the fever period were tested between the first and third weeks, and observed lying absolutely quiet on their backs throughout the procedure. Examinations were not begun until the pulse showed a constant rate, so that the psychic influence was avoided.

13. Burgusch and Schittenhelm: Technik d. speciel. klin. Untersuchungsmethoden, Part 2, p. 896.

We injected, in turn, atropin, epinephrin and pilocarpin, with an interval of from one to two days between them.

Standard for Test.—The standard of criticism, whether the result of the pharmacodynamic test is positive or negative, must be shown. It is a self-evident fact that the drugs we used are poisons and therefore have some action even on the healthy who have no abnormal tonus or irritability in their vegetative nervous systems. When reaction is very strong in comparison to doses, there is no doubt that the result is positive.

Atropin: When 0.001 gm. atropin was injected, the disturbance of salivation, mydriasis and decreased tonus of stomach and intestine would be expected theoretically, but these symptoms are not constant; consequently, we must rely on a change of heart function (Burgusch and Schittenhelm[18]). Eppinger and Hess demonstrated double increase of pulse rate, sometimes accompanied by palpitation, as a strong atropin action. Petrén and Thorling counted as positive those who had, in addition to thirst or palpitation, an increase of more than 20 in pulse rate. Lehmann considered the test as positive when there was an increase of 30 in the pulse rate, accompanied by thirst or palpitation, or when it was the only symptom an increase of pulse rate of more than 30. We counted it positive, as did Petrén and Thorling, when there was an increase of more than 20 in pulse rate, expressed by +, when more than 30 by ++; secondly, thirst and palpitation were taken into consideration. When the increase was 17 or 18 beats, if accompanied by increased thirst or palpitation, it was counted as positive; if not, as negative.

Epinephrin: When 0.001 epinephrin was administered, even in the healthy, after from five to ten minutes, palpitation, pallor, slight tremor, increase of pulse rate and elevation of blood pressure could be seen (Burgusch and Schittenhelm). Eppinger and Hess described excretion of more than 5 gm. glucose (100 gm. glucose were given before), double the quantity of urine, one third increase in pulse rate and increase of reflexes as a strong reaction to epinephrin. Petrén and Thorling, and Bauer did not show the standard clearly. Lehmann counted as positive more than 30 increase of pulse rate, more than 3 gm. glucose in urine (100 gm. glucose were given before) and marked tremor. We counted positive more than 20 increase of pulse rate, more than 20 mm. Hg increase of blood pressure, marked tremor, considerable palpitation and glycosuria (no previous administration of glucose). When more than two symptoms were observed and they were strong, we marked them + or ++, according to their strength. When the only symptom was increase of pulse rate or elevation of blood pressure, we counted it as negative unless the increase was more than 30. Glycosuria alone, on the contrary, counted as positive.

Pilocarpin: When 0.007 pilocarpin was injected, even in the healthy, after from five to seven minutes, salivation and sweating were noticed. The pulse ought to be decreased theoretically, but was found increased practically (Burgusch and Schittenhelm). Eppinger and Hess considered as a strong pilocarpin reaction, profuse salivation and profuse sweating. Lehmann laid chief stress on salivation, less on sweating and other symptoms. He put no value on increase of pulse rate. We considered sweating and salivation, when profuse and of long duration, as positive. Gastro-intestinal symptoms were also looked on as significant. When either sweating or salivation alone existed, we considered it negative, unless accompanied by gastric and intestinal symptoms.

EXPERIMENTS

Atropin: The action of atropin was examined in forty-six cases. A noteworthy phenomenon after injection was the paradoxical action, namely, from five to fifteen minutes after injection the pulse rate decreased. The pulse decrease was 3 in four cases, 4 in three cases, 5 in four cases, 6 in three cases and 7 in one case. After this decrease the pulse rate sometimes increased remarkably, but at others remained in the decreased condition. The most remarkable was Case 5, which showed a decrease of 17 in pulse rate after injection, accompanied by arrhythmia, and Aschner's bulbus phenomenon was also observed. Bauer had already described this paradoxical phenomenon, accompanied also by arrhythmia, only when small doses were given (0.0001 to 0.0002 of atropin), and that both bradycardia and arrhythmia disappeared when relatively large doses were given (0.0005). We, however, observed such a phenomenon by injecting 0.001, the same as Lehmann. A striking increase of pulse rate was seen in the following cases: 49 in Case 46, 39 in Case 14, 38 in Case 9, 32 in Case 13, 31 in Case 15 and 30 in Case 8; increase between 20 and 29 in six cases, 10 and 19 in fourteen cases and 0 and 9 in nine cases. It must also be noticed that increase of more than 30 pulse rate all occurred in youths (aged from 14 to 19). Eppinger and Hess said that the vagotonic condition was observed mostly in youths.

Lehmann also wrote that youth is sensitive to atropin. We show the relation in Table 1 to make the matter clearer.

TABLE 1.—Relation of Age and Sensitiveness to Atropin

Age	Cases Observed	Positive Reaction
14 to 19	16	10
20 to 29	12	5
30 to 39	13	3
40 to 67	5	3
Total	46	21

Here we must record the investigation published by Marris,[14] who reports that in practically all cases of the typhoid group during some period of the infection (mostly the second week), the rate of the heart cannot be accelerated by atropin as it can be in normal people and those suffering from other diseases, and uses this reaction as a means of diagnosis.

In our forty-six cases of typhoid fever (including seven cases of paratyphoid B), however, atropin was quite active, accelerating the rate of pulse, especially in cases of bradycardia. As all our cases were serologically and bacteriologically controlled, the diagnosis was undoubtedly correct.

All cases were tested during the fever period (between the sixth and the twenty-third day), and every possible precaution was also taken during the procedure.

The conditions were apparently the same as in the cases of Marris, notwithstanding that our results were evidently not in accord with his findings, for which we can give no satisfactory explanation at present.

Epinephrin: In 46 cases the action of epinephrin was examined. Epinephrin injection always accelerated the pulse, and no paradoxical phenomenon was observed. Remarkable increases were noticed as follows: 56 in Case 46, 52 in Case 40, 42 in Case 11, 35 in Case 10, from 20 to 29 in nineteen cases, from 10 to 19 in sixteen cases and from 2 to 9 in seven cases. The blood pressure was also always elevated. There were increases of 41 mm. in Case 36, 37 in Case 7, from 20 to 30 in thirteen cases, from 10 to 19 in nineteen cases and from 0 to 9 in ten cases. The respirations also accelerated after injection, as Bauer observed: increases of 11 in one case, 8 in three cases, 6 in three cases, 5 in five cases and 4 in eight cases.

In regard to temperature, any change that occurs immediately, namely, from 5 to 10 minutes after the injection, must be due to the epinephrin action. Increase of 0.8 C. in 1 case, 0.7 in 1 case, 0.6 in 1 case, 0.5 in 3 cases and 0.4 in 2 cases were observed. Epinephrin glycosuria was observed in 8 cases out of 45; tremor in 18 cases, mostly in the hand; palpitation in 15 cases; general lassitude, nausea and headache in some cases.

As Bauer and Lehmann observed, epinephrin does not act the same on every person. They called this condition dissociation of drug action. This dissociation was evident also in our cases. Table 2 shows the facts clearly:

14. Marris: Brit. Med. Jour., 1916, **2**, 717.

TABLE 2.—Dissociation of Drug Action After Epinephrin

Cases	
1	Glycosuria; elevation* of blood pressure; increase of pulse rate
1	Glycosuria; elevation of blood pressure
3	Glycosuria; increase of pulse rate
3	Glycosuria
8	Elevation of blood pressure; increase of pulse rate
5	Elevation of blood pressure
10	Increase of pulse rate

*By increase or elevation we mean more than 20 in pulse rate or more than 20 mm. of mercury in blood pressure, respectively.

As the table shows, three symptoms were observed in one case only.

Eppinger and Hess noticed that sympathicotonia is often seen in old people, while Lehmann, on the contrary, stated that youth is sensitive to epinephrin. In our experiments we noticed no relation between sensitiveness to epinephrin and age, as shown by Table 3.

TABLE 3.—Relation of Age and Sensitiveness to Epinephrin

Age	Cases Observed	Positive Reaction
14 to 19	16	9
20 to 29	12	6
30 to 39	13	9
40 to 67	5	2
Total.....	46	26

Pilocarpin: Pilocarpin was tested in thirty-eight cases. Pilocarpin decreases the pulse rate in animal experiments, but on the human body, on the contrary, it has no such effect (Eppinger and Hess). Bauer and Lehmann even maintained that it caused an increase.

It must be noticed in Case 9, in which, after injection of 0.007 pilocarpin, besides profuse salivation and sweating, the pulse rate decreased 14 within five minutes and returned to normal after nineteen minutes. Arrhythmia was observed at the same time. This fact, which nobody has as yet described, is very significant and interesting. In all other cases except Case 9 the pulse rate increased after injection: increases of 42 in Case 15, 37 in Case 13, 36 in Case 3, 33 in Case 11, 30 in Case 14, and from 20 to 29 in eleven cases, from 10 to 19 in fifteen cases and from 2 to 9 in nine cases.

Gastro-intestinal symptoms were seldom observed: nausea in two cases, vomiting in one case, gurgling of intestine in two cases and singultus in two cases.

Salivation and sweating began in sensitive cases five minutes after injection and lasted one hour. They almost always go hand in hand; however, there are some cases in which there is profuse salivation with very little sweating (Cases 27 and 38), and cases in which there is profuse sweating with no salivation (Cases 23, 26 and 36).

Thus, dissociation was observed even in pilocarpin action, as Bauer had already noted, but not so remarkable as in the case of epinephrin.

There is no relation between the action of pilocarpin and age. Table 4 shows the fact.

TABLE 4.—Showing Absence of Relation Between Age and Action of Pilocarpin

Age	Cases Observed	Positive Reaction
14 to 19	13	11
20 to 29	10	6
30 to 39	11	7
40 to 67	4	3
Total	38	27

DISCUSSION

The pharmacodynamic test of the vegetative nervous system in the fever period of typhoid fever was examined in forty-six cases in all.

In thirty-eight of them, atropin, pilocarpin and epinephrin were tested, and in eight cases atropin and epinephrin. The results we obtained from the thirty-eight cases may be classified as in Table 5.

TABLE 5.—Reactions to Atropin, Pilocarpin and Epinephrin

Reactions	Group	Cases Observed
Sensitive to atropin and pilocarpin; nonsensitive to epinephrin	1	14
Sensitive to epinephrin; nonsensitive to atropin and pilocarpin	2	11
Sensitive to atropin, pilocarpin and epinephrin	3	3
Sensitive to pilocarpin and epinephrin	4	7
Sensitive to pilocarpin	5	3

The first group in Table 5 corresponds to vagotonia, the second to sympathicotonia according to Eppinger and Hess. The third group is thought to be sympathetic and autonomic in elevated tonus, as once observed by Eppinger, Hess and Pötzl in cases of psychosis. The fourth group is the condition of heightened irritability of sympathetic and autonomic as often observed by Bauer and Lehmann. The fifth group is considered to be autonomic in elevated irritability.

The principal objections which were made by Petrén and Thorling, Bauer, and Lehmann to the opinion of Eppinger and Hess consist of the following two points: first, there are cases which are sensitive to both pilocarpin and epinephrin; second, atropin and pilocarpin do not act in parallel. Some of our experiments also confirmed this objection, namely, Group 4 shows sensibility to both epinephrin and pilocarpin, and Groups 4 and 5 show no parallelism between the action of atropin and pilocarpin.

We cannot, however, entirely agree with those who give up thereby the significant hypothesis of Eppinger and Hess. Quite a number of cases in such a state, namely, vagotonia and sympathicotonia, were confirmed by us.

Now let us assume the formula which was given by Liebermeister,[15] of counting the pulse rate from the body temperature: Rate of pulse $= 80 + 8\times (T - 37)$; T is the number read on the thermometer.

By means of this formula, we obtain the pulse rate corresponding to body temperature at the time of examination, and comparing this number with the true pulse rate, we know the relative bradycardia; that is, the more difference there is between pulse calculated and observed, the more pronounced the bradycardia.

Arranging our thirty-eight cases in order of relative bradycardia (Table 6), the following significant and important fact is found, namely, the cases of Group 1 (vagotonia) are placed in the upper spaces of the table, while those of Group 2 (sympathicotonia) are placed in the lower spaces. In other words, in cases of typhoid fever, a patient who has a significant bradycardia is mostly sensitive to atropin and pilocarpin, and one who has no bradycardia is mostly sensitive to epinephrin. Only those who have marked bradycardia are especially sensitive to atropin.

Supposing the bradycardia in typhoid fever were due to loss of equilibrium between sympathetic and autonomic, we may consider several possibilities; for instance, such a condition may be expected in abnormally elevated tonus of autonomic, or diminished tonus of sympathetic, or by stimulating autonomic only. The action of typhoid toxin for sympathetic and autonomic is not quite obvious. According to our experiments, however, we proved that 60 per cent. of marked bradycardia in typhoid fever is in the state of vagotonia; thus the so-called vagotonia may be considered as one cause of typhoid bradycardia.

Wenckebach[16] described recently in his book two kinds of bradycardia; one, cardial bradycardia, which is not accompanied by arrhythmia; the other, vagal bradycardia, which is always accompanied by arrhythmia. He also mentioned one case of bradycardia in typhoid fever which was of a vagal nature, and Pierret and Dartevelle[17] also found a similar case. Though their observations were made from the standpoint of arrhythmia, and ours from pharmacodynamic test, the results unexpectedly coincided.

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15. Liebermeister: Cited in Daten u. Tabellen, Vierordt, 1893, p. 156.

16. Wenckebach: Die unregelmässige Hertztätigkeit u. ihre klin. Bedeutung, 1914, p. 192.

17. Pierret and Dartevelle: Cited in Wenckebach (Footnote 16).

TABLE 6.—Summary of Authors' Observations

Group	Number of Cases	Age	Sex	Body Temperature, C.	Pulse Observed	Pulse Calculated	Relative Bradycardia	Atropin Reaction	Epinephrin Reaction	Pilocarpin Reaction	Deaths
3	14*	15	♂	38.0	56	88	32	++	+++	+	
1	9	16	♂	39.3	67	98	30	++	—	++	
1	4	68	♀	39.1	68	97	29	++	—	++	
4	11	33	♂	39.0	71	96	25	—	+++	+	
1	15	16	♂	39.0	73	96	23	++	—	++	
1	5	20	♂	39.4	77	99	22	++	±	++	
1	2	19	♂	39.6	80	101	21	+	—	+++	
2	25	21	♂	38.9	74	95	21	±	+	—	-
1	8	14	♂	39.7	85	102	17	++	—	++	
4	10	44	♂	38.3	73	90	17	—	+	+	
1	32	35	♂	38.6	79	93	14	+	±	+	
4	37	15	♂	39.4	85	99	14	—	+	+	
2	30	21	♂	39.1	83	97	14	—	+	—	-
1	17	22	♂	39.3	86	99	13	+	—	++	
1	3	15	♂	39.0	86	96	10	+	—	+	
1	12	24	♂	39.1	87	97	10	+	—	+	
1	13*	16	♂	37.8	76	86	10	++	±	+	
1	31*	23	♂	40.3	98	107	9	+	—	+	
1	19	40	♂	39.1	88	97	9	+	—	+	
3	24	31	♂	38.7	85	94	9	+	++	+	
1	1	26	♀	38.5	84	92	8	+	±	++	
4	6	32	♂	39.9	96	102	8	—	+	+	
2	36*	34	♂	38.9	88	96	8	—	++	±	
4	16	20	♂	39.3	92	98	6	±	+	+	
2	27	36	♂	39.5	94	100	6	—	++	—	-
2	26	24	♂	39.3	93	98	6	—	+	—	-
2	23	48	♀	39.7	98	102	4	—	+	—	
4	7	19	♂	38.7	90	94	4	—	++	++	
2	21	17	♂	39.2	95	98	3	—	+	—	
3	18*	16	♂	39.5	100	100	0	+	+	+	
5	20	36	♀	38.3	90	90	0	—	—	+	
2	29	18	♂	39.5	104	100	4†	—	+	—	
5	28*	15	♂	39.9	108	103	5†	—	—	+	
2	33	34	♀	39.5	106	100	6†	—	++	±	-
2	33	21	♀	39.5	106	100	6†	—	+	—	
2	22	14	♀	39.2	108	98	10†	—	+	—	
4	24	38	♀	38.8	104	94	10†	—	+	+	
5	35	32	♂	39.1	107	97	10†	—	±	++	

* Cases of Paratyphus B. † Tachycardia.

Another interesting fact is that our five fatal cases out of thirty-eight were all in the state of sympathicotonia, and one incurable patient out of eight tested for atropin and epinephrin reactions, was sensitive to epinephrin and nonsensitive to atropin.

It is a well known fact that in typhoid fever a rapid pulse signifies a doubtful prognosis. This fact has been ascertained by long experience and coincides with the result of our investigation. Furthermore, we already knew that the state of sympathicotonia is often seen in patients with a rapid pulse. We may also say that even in cases of bradycardia nonsensitive to atropin and pilocarpin, and sensitive to epinephrin, the prognosis is not good (Cases 25 and 30). This fact, which must be confirmed by repeated experiments, may be of some significance in establishing the prognosis of typhoid fever. Consequently, the examination of the functions of the vegetative nervous system in typhoid fever is indispensable.

SUMMARY

1. In typhoid cases, atropin acts strongly on those patients who have marked bradycardia, but has almost no effect on those who have no bradycardia. Increase of pulse rate is the most significant atropin action; then comes increase of thirst, and lastly palpitation. In only one case the remarkable paradoxical phenomenon, decrease of 17 in pulse rate, accompanied by arrhythmia, was observed.

2. After injection of epinephrin, increase of pulse rate, elevation of blood pressure, acceleration of respiration and elevation of body temperature were observed in many cases. Tremor and glycosuria were often observed, but palpitation, nausea, and headache seldom.

So-called dissociation of epinephrin action was observed even in cases of typhoid fever.

3. In the majority of cases salivation and sweating were observed after pilocarpin injection, besides nausea, vomiting and singultus. In only one case were we able to find a decrease of 14 in the pulse rate, accompanied by arrhythmia. This fact has never been noticed by anybody up to this time. Dissociation may be seen after pilocarpin in typhoid fever, but not so marked as after epinephrin.

4. According to our experiments, though youth is sensitive to atropin, no relation is to be seen between the action of epinephrin and age or pilocarpin and age.

5. Examining the function of the vegetative nervous system in 38 cases of typhoid fever, we found 14 cases which corresponded to vagotonia, 11 cases which corresponded to sympathicotonia, 3 cases which

were sensitive to all three drugs, 7 cases which were sensitive to pilocarpin and epinephrin, and 3 cases which were sensitive only to pilocarpin.

6. Though the cases supporting the objections made by Bauer and Lehmann are not rare, still in the majority of typhoid fever cases the state of vagotonia or sympathicotonia exists, which fact conforms with the opinion of Eppinger and Hess.

7. In the cases with marked bradycardia, the state of vagotonia was often observed, while in those with no bradycardia, sympathicotonia was often observed.

8. The state of vagotonia may be one explanation for bradycardia in typhoid fever.

9. The deaths in our cases were all in the condition of sympathicotonia. This fact may form the basis for establishing a prognosis in typhoid fever.

THE ACTION OF TYRAMIN ON THE CIRCULATION OF MAN *

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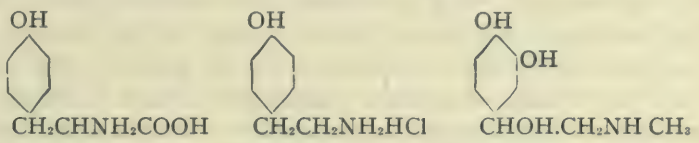
Tyramin is a hydrochloric acid salt of parahydroxyphenylethylamin. The latter is the most active blood pressure raising constituent in watery extracts of ergot.[1] It has been isolated from putrid meat[2] and from other decomposing organic substances. Here it appears to be formed by the action of bacterial ferments on tyrosin, one of the common amino-acid building stones of the protein molecule. The structural relationship of tyramin to tyrosin and to the physiologically related epinephrin is shown in the following structural formula:



Tyrosin Tyramin Epinephrin

The action of tyramin on the circulation of animals was studied by Dale and Dixon,[3] who found that the intravenous injection of 1 mg. into the cat or into other laboratory animals was followed by a sudden and marked rise of arterial blood pressure, reminiscent of that produced by epinephrin. As compared with the latter, however, the blood pressure changes showed a longer latent period, the rise to the maximum was less sudden and the decline to the original level was more gradual. Cardiometer tracings taken by these authors showed that the rise of blood pressure was associated with an increase in the amplitude of the ventricular beats. This occurred even when the slowing of the heart was eliminated by section of the vagus nerves or by their functional exclusion with atropin. Apparently, therefore, the heightened blood pressure was due in part to an increased output from the heart.

Dale and Dixon also found that tyramin constricted the systemic blood vessels. Volume tracings from the dog's ear, from a loop of

* Submitted for publication Jan. 9, 1918.

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1. Barger, G., and Dale, H. H.: The Water-Soluble Active Principles of Ergot, Proc. Physiol. Soc., May 15, 1909; Jour. Physiol., 1909, **38,** 77.

2. Barger, G., and Wampole, G. S.: Isolation of the Pressor Principles of Putrid Meat, Jour. Physiol., 1909, **38,** 343.

3. Dale, H. H., and Dixon, W. E.: The Action of Pressor Amines Produced by Putrefaction, Jour. Physiol., 1909, **39,** 25.

the cat's intestine and from the hind extremity showed a shrinkage of these organs when the drug was injected. Furthermore, the addition of tyramin to the fluid used in perfusing the cat's hind limb and the dog's small intestine caused a marked slowing of the flow through these organs. The pulmonary vessels, on the other hand, were not constricted by tyramin. From these observations it would appear that the rise of blood pressure produced by the intravenous injection of tyramin into laboratory animals was due not only to an increased output from the heart, but also to a constriction of the peripheral blood vessels.

Tyramin, like epinephrin, appears to act only on such muscle fibers and gland cells as receive a sympathetic nerve supply. According to Dale and Dixon, the effects produced on these structures, whether stimulating or inhibiting, are comparable to those produced by excitation of the sympathetic nerves themselves. Although the action of tyramin resembles that of epinephrin in this particular, the two actions are not identical. Not only is tyramin much less active, being about one twentieth as powerful when judged by its pressor effects, but qualitative differences between the two drugs also exist. Thus Baehr and Pick[4] found that while epinephrin caused a dilatation of the bronchi, tyramin caused a constriction. With respect to the blood vessels, it has been noted that epinephrin produces a much greater local effect. Thus Sollmann and Pilcher[5] found that the application of epinephrin to slight cutaneous abrasions caused marked local pallor, whereas tyramin was without effect. Furthermore, tyramin has no value as a local hemostatic. The constriction of the blood vessels about subcutaneous or intramuscular injections of epinephrin interfere with its absorption into the general circulation, and this is believed to account for the fact that such injections rarely produce the marked rises of blood pressure that follow intravenous administration of epinephrin. On the other hand, tyramin with its less marked local effect, usually causes a striking elevation of the blood pressure when injected subcutaneously.

EFFECT ON THE BLOOD PRESSURE AND PULSE RATE OF MAN

The effect of tyramin on the circulation of man was tested by Dale and Dixon, one of whom took 10 mg. of the drug by mouth. The moderate rise of systolic pressure which was observed in this experiment was probably due to some cause other than the drug given; for

4. Baehr, G., and Pick, E. P.: Pharmakologische Studien an der Bronchialmuskulatur der überlebenden Meerschweinchenlunge, Arch. f. exper. Path. u. Pharmakol., 1913, **74**, 41.

5. Sollmann, T., and Pilcher, J. D.: Endermic Reactions, Jour. Pharm. and Exper. Therap., 1917, **9**, 309.

Clark[6] showed subsequently that much larger doses — up to 200 mg. within forty minutes — when given by mouth, produced no striking effect on the blood pressure. If, however, tyramin were injected into man subcutaneously, it produced, in most instances, unmistakable circulatory effects. Clark,[6] Hoyt,[7] and Watson,[8] each of whom studied the effect of subcutaneous injections on the blood pressure of man, found that tyramin usually caused a marked elevation of the systolic blood pressure. This rise usually began within a few (two to ten) minutes, proceeded rapidly to its maximum and then fell somewhat more slowly to the original level. The whole reaction occupied a period of fifteen to thirty minutes or more. In order to produce an appreciable rise of pressure, 20 mg. must ordinarily be injected. Larger doses (60 to 80 mg.) may cause very considerable elevations of pressure. Watson,[8] who recorded the diastolic as well as the systolic pressure, found that the former was not affected by the drug, the heightened systolic pressure being due entirely to an increase in the pressure amplitude or pulse pressure. When the systolic blood pressure rose, the pulse rate usually fell, presumably because the heightened blood pressure caused a vagus inhibition of the heart.

In the present series of observations tyramin was administered subcutaneously in doses of from 40 to 80 mg., the usual dose being 60 mg. The resultant changes in the systolic blood pressure and the pulse rate were similar to those described by the authors just cited. In most instances the injection was followed within a few minutes by a striking rise in the systolic blood pressure and by a slowing of the pulse. Illustrative curves are shown in Figure 1. From this figure it may be seen that the rise in systolic pressure began within five minutes after the injection, that the maximum elevation usually occurred within ten minutes after the injection, and that the blood pressure had usually returned to the normal in from twenty to thirty minutes. Although Watson stated that the diastolic pressure was not affected by the drug, our observations indicate that in the doses given there was usually a slight but definite rise in the diastolic pressure. This, however, was very much less than the rise in systolic blood pressure, so that there was a marked increase in the pulse pressure. It is noteworthy also that the vascular sounds heard during the auscultatory determinations of blood pressure became much louder at the height of the tyramin action.

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6. Clark, A.: The Clinical Application of Ergotamine, Biochem. Jour., 1910-1911, **5,** 236.

7. Hoyt, D. M.: The Therapeutic Application of P. Hydroxyphenylethylamin (Tyramine); an Active Principle of Ergot, Am. Jour. Med. Sc., 1912, **144,** 76.

8. Watson, A.: Observations on the Value of Drugs as Blood Pressure Elevators, Practitioner, London, 1915, **94,** 566.

The foregoing changes in the systolic blood pressure occurred in almost every instance when tyramin was injected in doses of 40 mg. or more (Tables 1 and 2). Yet no very definite relation existed between the rise of pressure and the dose of drug administered. In two persons, indeed, no rise of systolic pressure was observed. The cause of such variations in the effect of the drug is not certain. Aside from variations in individual susceptibility, the rate of absorption from the site of injection probably played a considerable rôle in

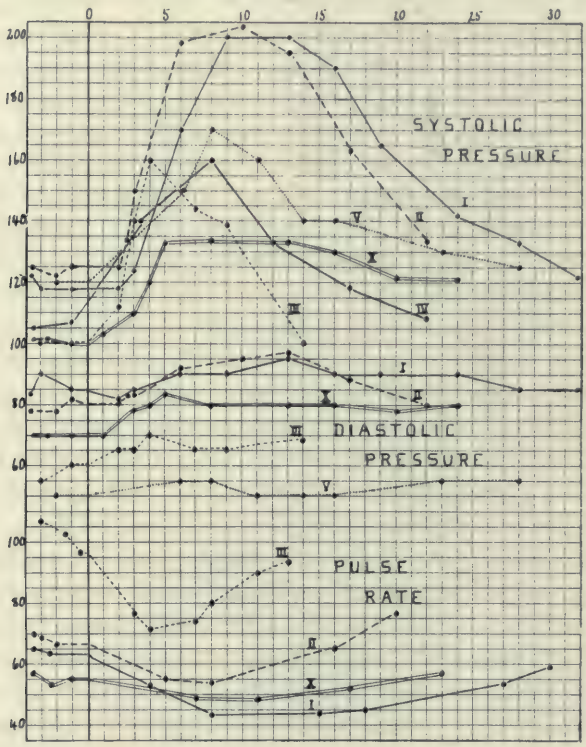

Fig. 1.—Chart showing the effect of tyramin on the systolic and diastolic blood pressure and on the pulse rate. The Roman numerals correspond to the cases in Table 1.

determining the intensity of the reaction. Clark stated that when injections were given into the arm or forearm little general reaction followed, and he recommended that injections be given into the loose tissues about the clavicles. In one of our tests without reaction a lump formed at the site of the injection in the forearm. Following Clark's suggestion, therefore, most of the remaining injections were given into the loose subcutaneous tissues beneath the clavicle.

Any marked rise of pressure was, as a rule, accompanied by a slowing of the pulse similar to that reported by others who have studied the clinical effects of the drug. From Dale and Dixon's animal experiments this appears to result from vagus stimulation by the heightened blood pressure. In two instances the pulse rate increased during the action of the drug. One of these patients (No. 13) had exophthalmic goiter and the pulse rate increased from 75 to a maxi-

TABLE 1.—EFFECT OF TYRAMIN ON BLOOD PRESSURE, PULSE RATE AND VOLUME PULSE

Case	Hospital Number		Dose, Gm.	Blood Pressure			Pulse Rate	Volume Pulse	Sustained Quality
				Systolic	Diastolic	Pulse			
1	59747	Before		118	85	33	64	0.39	
		After	0.06	200	92	108	44	0.68	Increased
2	59947	Before		125	79	46	68	0.65	
		After	0.065	203	95	108	54	0.70	No change
3	60120	Before		100	57	43	100	0.90	
		After	0.06	160	70	90	72	1.2	Increased
4	57928	Before		106	..	..	..	0.55	
		After	0.06	160	..	..	..	1.0	Increased
5	58322	Before		120	50	70	..	1.20	
		After	0.08	170	52	118	..	1.48	No change
6	57783	Before		120	72	48	..	0.55	
		After	0.04	170	83	87	..	0.69	Increased
7	57676	Before		131	80	51	..	0.85	
		After	0.05	180	84	96	..	1.25	No change
8	59876	Before		120	82	38	57	0.47	
		After	0.06	165	90	75	45	0.60	No change
9	58051	Before		115	85	30	..	0.88	
		After	0.05	155	90	65	..	1.05	Increased
10	59732	Before		100	70	30	55	1.10	
		After	0.06	134	80	54	48	0.90	No change
11	59732	Before		113	86	27	56	0.92	
		After	0.06	134	90	44	52	0.95	No change
12	59856	Before		155	85	70	107	0.72	
		After	0.05	180	85	95	94	0.87	No change

mum of 84. The other patient (No. 16) showed extrasystoles before the administration. This irregularity became more pronounced and at the same time the sinus rate was accelerated (Fig. 6). In the remaining tests any marked rise of systolic pressure was accompanied by a definite slowing of the heart rate, which disappeared as the pressure fell to normal.

EFFECT ON THE VOLUME PULSE IN THE ARM

In twelve experiments the volume pulse of the forearm and lower arm was recorded by using a plethysmograph which was connected with a Frank capsule by air transmission. Calibration was made in

each experiment by introducing into or withdrawing from the plethysmograph 2 c.c. of air while the arm was in place. The average change on the records produced by several such tests was taken to indicate the effect resulting from a 2 c.c. change in arm volume.

Table 1 shows that in nine of the twelve experiments a distinct increase (over 0.1 c.c.) in the size of the volume pulse in the arm

Fig. 2.—The volume pulse in the arm after tyramin. (Case 1 of Table 1 and Figure 1.) First record taken before, second 4 minutes after, third 8 minutes after, fourth 15 minutes after, fifth 18 minutes after and last 30 minutes after the injection of 0.06 gm. tyramin. The changes in the size and form of the pulse waves were most marked in the third and fourth records.

occurred at the height of the tyramin action; in two instances the recorded increase was so slight as to be doubtful, while in one instance the volume pulse was distinctly lessened. This increase in the volume

of the arm pulse was, as we shall see, presumably due to a larger output of blood at each cardiac systole.

The form of the volume pulse was altered in five of the twelve experiments, and in each case this alteration was in the direction of a more sustained pulse. In Figure 2, for example, the primary pulse wave was followed by an anacrotic plateau at the height of the tyramin effect. In Figure 3 from a patient with typhoid fever, the collapsing quality of the febrile pulse became less marked. Such changes were not constant, however, and in many instances no definite alteration in the form of the arm pulse was noted during the heightened systolic pressure and slow pulse produced by the tyramin injection.

In four instances satisfactory records of the blood flow in the arm were obtained. These showed no marked and constant alteration. In

TABLE 2.—EFFECT OF TYRAMIN ON THE ELECTROCARDIOGRAM

Case	Hospital Number		Dose, Gm.	Systolic Pressure	Pulse Rate	Lead I P R T	Lead II P R T	Lead III P R T
13	56167	Before		110	75	1.0 6.0 1.0	1.2 18.0 0.5	0.5 15 0.0
		After	0.06	162	82	0.0 6.5 4.0	1.5 20.0 5.0	1.8 17 1.5
14	57676	Before		113	85	0.2 3.0 1.7	2.5 9.0 2.0	2.2 7 0.5
		After	0.05	140	80	0.2 3.0 2.0	2.5 9.0 5.2	2.5 6 2.5
15	58845	Before		135	90*	0.8 5.5 1.7	2.0 12.0 1.3	1.0 7 0.0
		After	0.06	160	106*	0.3 4.5 2.7	2.8 11.0 2.5	2.0 7 0.5
16	57928	Before		102	84	1.0 9.5 3.0	0.7 16.0 2.5	0.5 8
		After	0.06	130	73	0.7 8.0 5.0	0.7 15.0 4.8	0.3 9
17	.....	Before		135	63	No change		
		After	0.06	122	60			

* Sinus rate. Numerous ventricular extrasystoles occurred (Fig. 6).

one case no change occurred, in a second there was a slight increase during the heightened blood pressure, with a slight diminution when the pressure fell, while in the remaining two there was a gradual increase in the rate of flow, which continued after the pressure fell. Whatever may have been the cause of this gradual increase, it was not definitely related to the variations in the blood pressure.

EFFECT OF TYRAMIN ON THE ELECTROCARDIOGRAM

In five patients electrocardiograms were taken before the administration of tyramin and again at the height of the rise of blood pressure. The instrument was carefuly adjusted before each record with the patient in circuit so that a deflection of 10 mm. should correspond to a current of 1 milliampere. Of these five patients, one showed no rise of blood pressure after the injection and no change in the electrocardiogram. In the remaining four patients the change in blood

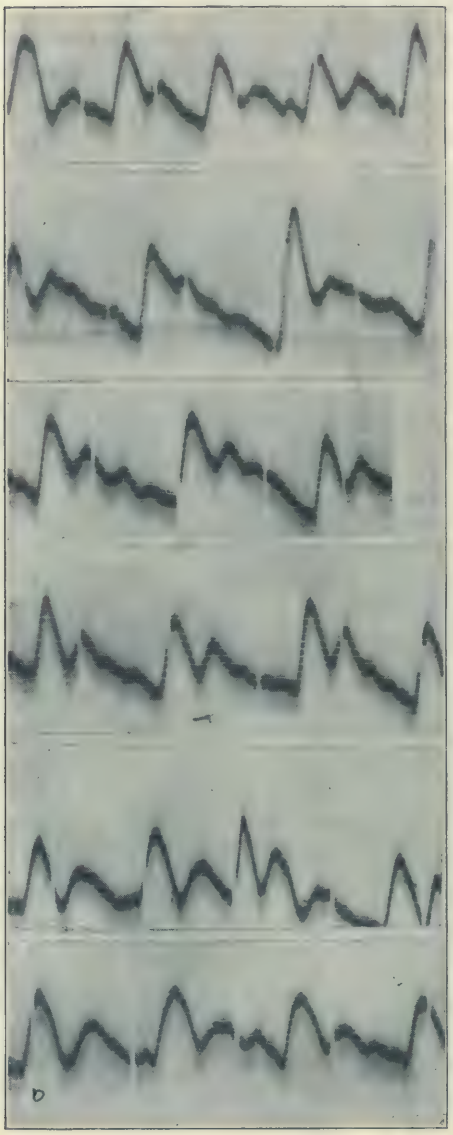

Fig. 3.—The volumes pulse in the arm after tyramin (Case 3 of Table 1 and Figure 1), a patient with typhoid fever. First record before, second 4 minutes after, third 7 minutes after, fourth 8 minutes after, fifth 11 minutes after and last 13 minutes after the injection of 0.06 gm. tyramin. The change in size and form of the pulse was most marked in the second and third records. In this patient the maximum effect occurred unusually early. A premature beat is seen in next to the last record.

pressure was accompanied by definite alterations in the form of the electrocardiogram. These may be seen by referring to Table 2 and to Figures 4, 5 and 6. The most constant of these changes was an increase in the size of T. This occurred in every instance in which T was originally upright. In one patient where T was originally small and diphasic in Lead III (Figure 5), it became somewhat more definite after tyramin, but the diphasic character of the wave did not permit of expressing the change numerically. In another patient, not included in Table 2 because the instrument had not been carefully calibrated before each record, T was negative in Lead III before the injection and it apparently became more so under the influence of tyramin.

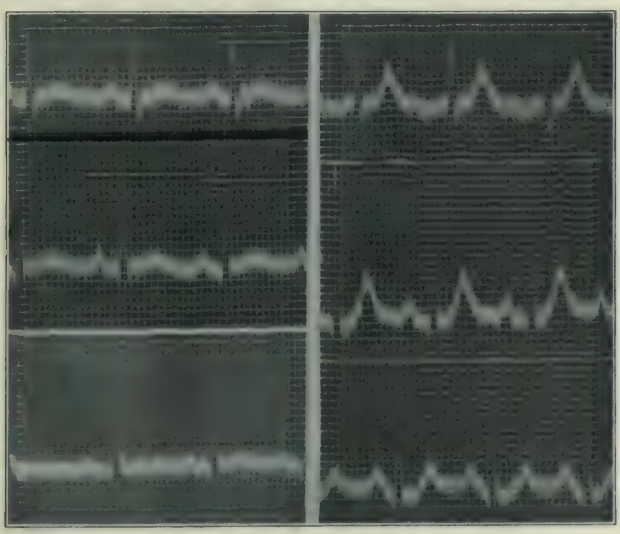

Fig 4.—Electrocardiograms taken before (left) and after (right) the injection of 0.06 gm. tyramin. (Case 13, Table 2.) T became larger in all leads; P became smaller in Lead I and larger in Lead III.

Changes in the other waves of the electrocardiogram, though present in certain instances, were not constant. The QRS complex was on the average unaffected. P showed a slight but not invariable tendency to be diminished in Lead I and increased in Lead III.

Augmentation of T has been described by Rothberger and Winterberg[9] after accelerator stimulation, and by Lewis and Cotton[10] and others following exercise. In these conditions, however, P also

9. Rothberger, J., and Winterberg, H.: Ueber die Beziehungen der Herznerven zur Form des Elektrokardiogramms, Arch. f. d. ges. Physiol., 1910, **135,** 506.

10. Lewis, T., and Cotton, T. F.: The "P-R" Interval in Human Electrocardiograms and Its Relation to Exercise, Proc. Physiol. Soc., June 28, 1913; Jour. Physiol., 1913, **46,** 60.

increased in size, whereas this did not occur after tyramin injections, except in Lead III.

THE PRODUCTION OF EXTRASYSTOLES

On four or five occasions it was noted that extrasystoles, previously absent, occurred during the action of tyramin. Such a premature beat is seen in next to the last tracing of Figure 3. Before this fact was fully appreciated, a patient already showing occasional ventricular extrasystoles was given an injection of tyramin in order to determine if this might influence the irregularity in a favorable manner. In place

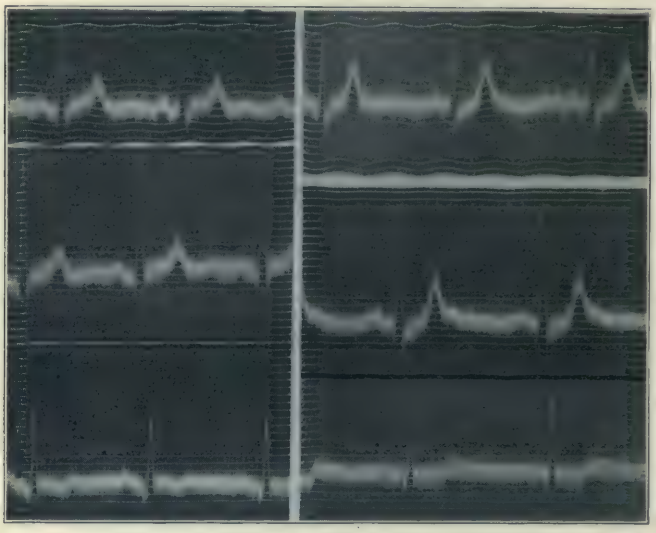

Fig. 5.—Electrocardiograms taken before (left) and after (right) the injection of 0.06 gm. tyramin. (Case 16, Table 2.)

of a favorable effect, there was an increase in the number and variety of abnormal ventricular contractions (Fig. 6).

Levy produced ventricular fibrillation in a cat under chloroform anesthesia by injecting tyramin.[11] Inasmuch as there is a close relationship between ventricular fibrillation and very numerous ventricular extrasystoles, it seems possible that under proper conditions tyramin might cause a dangerous or even fatal ventricular fibrillation in man. Caution is therefore urged in the use of this drug if ventricular extrasystoles are already present or if there is reason to suspect a condition

11. Levy, A. G.: The Genesis of Ventricular Extrasystoles Under Chloroform; with Special Reference to Consecutive Ventricular Fibrillation, Heart, 1913-1914, **4**, 299.

of increased irritability in the heart muscle such as seems to occur during chloroform anesthesia.

EFFECTS PRODUCED BY SUBCUTANEOUS INJECTIONS OF EPINEPHRIN

In susceptible individuals, subcutaneous injections of epinephrin frequently produce symptoms and signs which resemble those of exophthalmic goiter. Within a few minutes the individual experiences

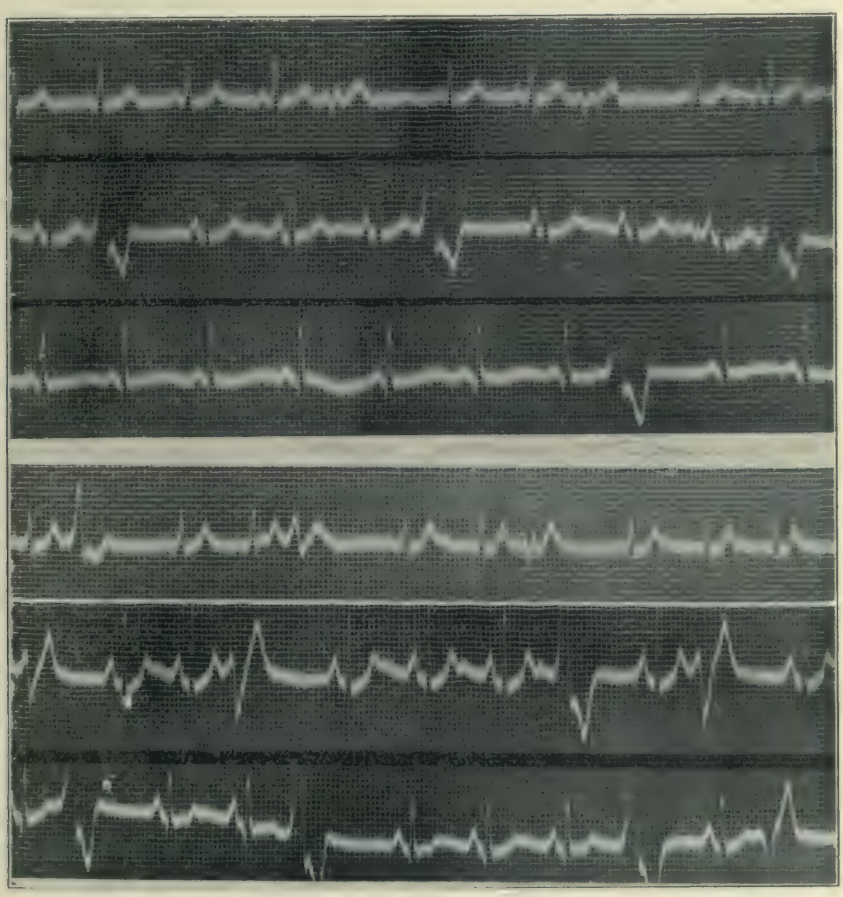

Fig. 6.—Increased number of extrasystoles caused by tyramin. Record above taken before and record below taken after the injection of 0.06 gm. (Case 15, Table 2.)

tremulous sensations which are demonstrable objectively as a tremor of the extended hands. This tremor seems to be somewhat coarser and less regular than is the typical tremor of exophthalmic goiter, and it frequently involves the arms as well as the hands and fingers. In

addition the susceptible person often feels anxious and nervous, and is conscious of palpitation and uneasy sensations about the precordium and epigastrium. Patients with exophthalmic goiter are particularly prone to exhibit distressing symptoms of this type after epinephrin injections, and several have said to the author that for the time being the usual symptoms of their disease became much worse. For this reason a considerable number of epinephrin injections were given to nervous persons with the hope that the degree of reaction might prove of some value in the diagnosis of incipient exophthalmic goiter. No

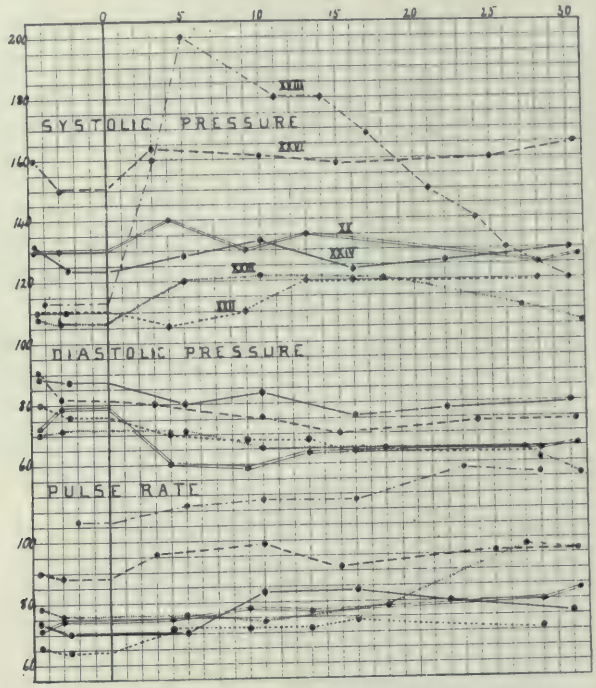

Fig. 7.—Chart showing the effect of subcutaneous injections of epinephrin on the systolic and diastolic blood pressure and on the pulse rate. The Roman numerals correspond to the cases in Table 3. The marked rise of blood pressure (Case 18) was in a patient with exophthalmic goiter. In this patient auricular extrasystoles also occurred; most numerous at sixteen minutes and less numerous at twenty-three and twenty-eight minutes after the injection.

definite relation was found, however, between susceptibility to epinephrin and the milder degrees of hyperthyroidism as judged clinically. In making these tests a number of records were made of the circulatory changes produced by subcutaneous injections of epinephrin. These will be reviewed briefly in order to contrast them with the circulatory changes induced by tyramin.

It is well known that the marked rise of blood pressure which occurs after the intravenous injection of a large dose of epinephrin is rarely observed when the drug is administered subcutaneously. The gradual absorption from the subcutaneous tissues, together with its destruction or disappearance in the tissues, prevents any marked rise in the concentration of epinephrin in the blood. Even though there is little or no rise in the blood pressure, nevertheless subcutaneous injections of epinephrin often produce definite physiologic effects in man. In addition to the tremor, nervousness and palpitation, we may mention the occasional production of glycosuria and the remarkable relief from asthmatic paroxysms that is often afforded by this drug. It is now known that in laboratory animals intravenous injections of small doses of epinephrin usually cause a fall of blood pressure and a dilatation of certain vascular areas, particularly those supplying the muscles in the extremities.[12] Analogous effects might be anticipated, when, owing to its subcutaneous administration to man, the absorption is slow.

Like others, we found that the changes in blood pressure after subcutaneous injections of epinephrin into patients varied considerably (Fig. 7 and Table 3). Occasionally there was a very marked rise in the systolic blood pressure similar to that produced by intravenous injections of the drug; but as a rule the systolic pressure rose only moderately or at times not at all. The diastolic pressure rarely rose.

In most cases it was either uninfluenced to any definite degree or it showed a distinct fall. Watson,[13] who was much impressed with this fall, suggested that inasmuch as "adrenalin had been proved so clearly to cause contraction of the peripheral vessels" the fall of diastolic pressure was attributable to a temporary aortic regurgitation. In the light of our present knowledge of the vasodilator action of epinephrin, however, it appears more reasonable to attribute the fall of diastolic pressure to vascular relaxation.

In our experience the most constant effect of this drug on the blood pressure was an increase in the difference between the systolic and diastolic pressures; that is, in the pulse pressure. There was also in almost every instance a very definite increase in the loudness of the

12. Cannon, W. B., and Lyman, H.: The Depressor Effect of Adrenalin on Arterial Pressure, Am. Jour. Physiol., 1913, **31,** 376. Hartman, F. A.: The Differential Effect of Adrenalin on Splanchnic and Peripheral Arteries, Am. Jour. Physiol., 1915, **41,** 513. Hoskins, R. G., Gunning, R. E. L., and Berry, E. L.: The Effect of Adrenin on the Distribution of the Blood, Am. Jour. Physiol., 1916, **42,** 513; 1917, **43,** 399. Hartman, F. A., and McPhedran, L.: Further Observations on the Differential Action of Adrenalin, Am. Jour. Physiol., 1917, **43,** 311.

13. Watson, A.: Some Observations on the Effect of Hypodermic Injections of Adrenalin on the Blood Pressure, Practitioner, London, 1914, **92,** 94.

vascular sounds which are heard below the pressure cuff during the auscultatory determinations of blood pressure.

The pulse rate after subcutaneous injections of epinephrin was usually somewhat increased (Fig. 7, Table 3). The volume pulse in the arm became larger (Table 3), and its form, while often unaltered, tended to become more collapsing (Table 3, Fig. 8). This change suggested a vascular relaxation in the arm. Unfortunately, no records

TABLE 3.—Effect of Subcutaneous Injection of Epinephrin

Case	Hospital Number		Dose, 1:1,000 Solution, Minims	Tremor	Blood Pressure			Pulse Rate	Volume Pulse	Sustained Quality
					Systolic	Diastolic	Pulse			
18	56167	Before		+	113	..	..	112		
		After	15	+++	200	..	..	124		
19	54169	Before		0	125	..	..	84	0.32	
		After	7	+++	155	80	75	104	0.86	Lessened
20	54276	Before		0	130	75	55	72	1.2	
		After	10	+	135	64	71	84	1.85	Lessened
21	53938	Before		..	...	..	..	...	0.9	
		After	10	..	...	..	..	...	1.5	Lessened
22	54718	Before		0	110	78	32	65	0.75	
		After	8	+	120	64	56	74	1.3	Lessened
23	54241	Before		+	106	71	35	76	0.85	
		After	10	+++	{122	65	57	74}	1.2	No change
					{105	50	55	96}		
24	54035	Before		0	128	88	40	72	0.6	
		After	10	+	{134	84	50}	84	0.9	Lessened
					{124	76	48}			
25	54263	Before		+	109	68	41	64	0.7	
		After	10	++	{108	70	38}	70	1.0	No change
					{104	64	40}			
26	54280	Before		+	155	85	69	89	0.8	
		After	10	++	{164	84	80}	96	1.0	Lessened
					{158	70	88}			
27	54745	Before		+	119	81	38	80	0.6	
		After	6	++	122	74	48	76	0.7	No change
28	17526	Before		+	128	88	40	82	1.1	
		After	7	+	122	84	38	82	1.2	No change

were made of the rate of blood flow through the arm before and after epinephrin injections.

A few electrocardiograms were taken before and after the injections. In some there was a distinct increase in T similar to that produced by tyramin; in others this change was slight or did not occur. This increase of T was most marked in a patient who also showed a striking rise of systolic pressure (Case 18), but its relation to the blood pressure changes was not further studied.

The circulatory alterations produced by tyramin, by epinephrin, by pituitary extract and by nitroglycerin are compared in Table 4. From this it will be seen[1] that tyramin resembles pituitary extract in that

both tend to raise the diastolic pressure and to cause a more sustained pulse, (2) that epinephrin resembles nitroglycerin in that both tend to lower the diastolic pressure and to cause a more collapsing pulse, while (3) tyramin and epinephrin resemble each other in that both cause a definite increase of pulse pressure, augmentation of T in the electrocardiogram and occasional extrasystoles.

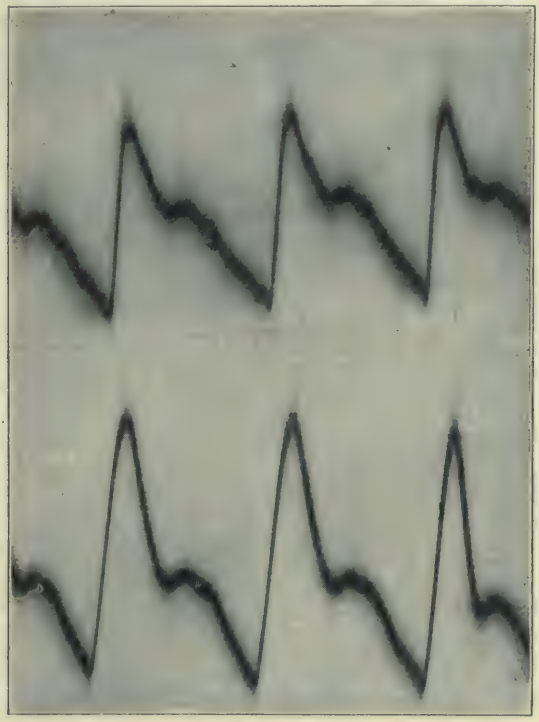

Fig. 8.—Volume pulse in the arm after the subcutaneous injection of 10 minims epinephrin solution (1 to 1,000). Upper before and lower twenty-four minutes after the injection. (Case 20 of Fig. 7 and Table 3.)

DISCUSSION

The most striking circulatory changes that we have observed in man after injections of tyramin may be summarized as follows:

(*a*) an increase in the systolic blood pressure, the pulse pressure and the volume pulse in the arm;

(*b*) a slowing of the heart rate, and

(*c*) an increase in the size of T in the electrocardiogram with the occasional occurrence of extrasystoles.

The increase in pulse pressure appears to be due mainly to an increased output of blood with each ventricular systole. It is true that an increased pulse pressure might conceivably result from a constriction or a heightened tone of the blood vessels. In such a case,

however, one would expect to find a far greater rise in the diastolic pressure than was actually observed. Furthermore, we know that certain drugs which act primarily on the blood vessels produce characteristic changes in the volume pulse of the arm. Nitroglycerin, a typical vasodilator, causes the arm pulse to become larger and more collapsing,[15] whereas pituitary extract, a typical vasoconstrictor, causes the collapsing pulse of febrile patients to become smaller and more

TABLE 4.—Comparison of the Usual Effects on Man of Pituitary Extract, Tyramin, Epinephrin and Nitroglycerin

	Pituitary Extract	Tyramin	Epinephrin	Ntroglycerin
Mode of administration	Intramuscularly	Subcutaneously	Subcutaneously	On tongue
Systolic pressure	No constant change[14]	Marked increase	Usual increase; varies from little change to marked increase	Diminished
Diastolic pressure	Increased[14] (febrile pulse)	Slight increase or no change	Diminished or no change	Diminished
Pulse pressure	Diminished[14] (febrile pulse)	Marked increase	Moderate increase	
Pulse rate	Occasional slight slowing[14]	Marked slowing	Some increase	Some increase[15]
Volume pulse in arm	Diminished[16] (febrile pulse)	Increased	Increased	Increased[15]
Sustained quality of arm pulse	More sustained[16] (febrile pulse)	More sustained or no change	Less sustained or no change	Less sustained[15]
T wave in electrocardiogram	No change	Augmented	No change or augmented	No change [15]
Tendency to produce ventricular extrasystoles	Apparently none	Present	Present[16]	None

sustained.[16] After tyramin the arm pulse becomes larger, but its form, if altered at all, is more sustained. Such a change is not typical of vascular constriction, and is more readily explained on the assumption that there is an increased systolic output from the heart.

Inasmuch as this increased output at each cardiac contraction is accompanied by a reduction in the heart rate, the question arises whether the total cardiac output in a unit of time is affected by tyramin. Our data do not furnish an accurate measure of the cardiac output. If this is roughly proportional to the product of heart rate × pulse pressure, then it would appear that tyramin materially increases the total cardiac output, for under its influence the above product is often

14. Schmidt, H. B.: The Effect of Pituitary Injections on the Blood Pressure of Febrile Patients, The Archives Int. Med., 1917, **19,** 1059.

15. Hewlett, A. W.: Van Zwaluwenburg, J. G., and Agnew, J. H.: The Pulse Flow in the Brachial Artery, The Archives Int Med., 1913, **12,** 7.

16. Hewlett, A. W.: The Pulse Flow in the Brachial Artery; the Influence of Certain Drugs, The Archives Int. Med., 1917, **20,** 1.

increased by 50 to 100 per cent. One must recognize, however, that various fallacies are possible in reasoning from these data. It is not our intention therefore to insist that tyramin, which has been demonstrated in animal experiments to possess a vasoconstrictor action, is without such an action when injected into man. We wish rather to point out that by the methods used an increased cardiac output seems probable, whereas vascular effects that were comparable to those produced by pituitary extract could not be demonstrated.

Subcutaneous injections of epinephrin also caused an increase in pulse pressure which was accompanied by a slight to moderate increase in the pulse rate. The product, heart rate × pulse pressure was therefore increased, and this may again be taken, with some reserve, to indicate that the cardiac output was increased by subcutaneous injections of this drug. As compared with tyramin, however, the action of epinephrin, injected subcutaneously, was characterized by evidence of vascular relaxation. In the first place, the diastolic blood pressure usually fell. In the second place, the arm pulse usually became larger and it often became more collapsing, changes that are comparable to those produced by the administration of nitroglycerin. This view that subcutaneous injections of epinephrin usually relax the blood vessels, particularly in the arm, is in accord with recent animal experiments which have demonstrated that small doses of epinephrin may reduce the blood pressure and that the drug in appropriate doses dilates various vascular areas, particularly those supplying the voluntary muscles and the intestines.[12]

Tyramin not only alters the heart rate and the systolic output, but it modifies the ventricular contractions in other ways, as is shown by the augmentation of T in the electrocardiogram and by the occasional production of ventricular extrasystoles. The cause of these changes has not been determined. Among their possible causes are mechanical alterations in the circulation owing to the increased systolic output and the heightened blood pressure, nervous influences such as accelerator stimulation in addition to the vagus inhibition, and finally, a direct effect of the drug on the ventricular muscle. We have pointed out that similar changes in the electrocardiogram as well as occasional ventricular extrasystoles have been induced by epinephrin. According to Levy[11] the ventricular irregularities produced in animals by epinephrin cannot be explained solely by the alterations of blood pressure and Roth[17] found no relation between the pressure changes and the ventricular extrasystoles induced in cardiac patients by epinephrin injections. By analogy, therefore, it would seem probable that the extrasystoles induced by tyramin are due in part to other causes than the changes in blood pressure and cardiac output.

17. Roth, O.: Ueber die Reaktion des Menschlichen Herzens auf Adrenalin, Deutsch. med. Wchnschr. 1914, **40,** 905.

OBSERVATIONS REGARDING THE LOSS OF WATER VAPOR THROUGH THE SKIN IN INFANTS*

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The elimination of heat from the body is dependent almost entirely on radiation, conduction and evaporation. While it is possible to determine the sum total of heat loss of an individual, the accurate determination of the parts entering into this sum is beset with difficulties which have not as yet been surmounted. Nevertheless, even relatively simple methods can yield some information, if not of the amount of heat lost by one or the other mechanism, at least about some of the conditions exercising an influence thereon. Thus, a study of the surface temperature gave us some data[1]— more accurate than available before — concerning the heat loss by conduction and radiation. In this communication we wish to report data with regard to the evaporation of water from the body surface other than the loss of water through lungs and sweat, that is, the so-called *insensible perspiration.*

The observations of Loewy,[2] made on individuals whose skin was devoid of sweat glands, would seem to demonstrate that insensible perspiration is entirely independent of the sweat glands.

Attempts to determine the amount of water eliminated from the skin in the form of insensible perspiration have been made by a considerable number of workers using various direct and indirect methods. The literature on the subject is excellently reviewed in the paper of Soderstrom and DuBois.[3] None of the direct methods seems to have been applied to the infant. In our review of the literature we were not able to find any work in which the loss of water through the skin was determined separately from that through the lungs. In infancy insensible perspiration would seem to be of special importance because the sweat glands usually do not functionate during this period of life. The determination of the insensible perspiration from the total skin surface would be most desirable. Such a procedure, if at all feasible,

* Submitted for publication Jan. 22, 1918.
* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.

1. McClure and Sauer: Am. Jour. Dis. Child., 1915, **10,** 425.
2. Loewy: Biochem. Ztschr., 1914, **67,** 243.
3. Soderstrom and Du Bois: THE ARCHIVES INT. MED., 1917, **19,** No. 5, Part II, p. 931.

would be very difficult indeed. Some data with regard to the loss of water from a restricted area of the skin were obtained, however, by a simple method kindly suggested to us by Prof. H. G. Gale of the Department of Physics of the University of Chicago. A current of room air was drawn over an area of skin and subsequently through a set of calcium chlorid tubes properly prepared. The air current was maintained by means of a water syphoning apparatus; the rate of flow was regulated readily by measuring the water withdrawn from the syphoning bottle during a unit of time. A rectangular metal box of 4.5 cm. depth and 7.5 by 5 cm. top was placed on the skin with the open bottom enclosing an area of 37.5 square centimeters. This box was placed on the chest, and a control box of exactly the same dimensions, but closed on all sides, was placed immediately next to it. The tubes for the entrance and exit of the air were at opposite ends of the boxes and at different levels, thus insuring better ventilation. The control box was also connected with calcium chlorid tubes and syphon. By this arrangement the conditions for control and experiment were as nearly alike as possible. Temperature and humidity of the room air were also determined. The calcium chlorid tubes of the two systems were weighed before and after each observation, the control giving the water absorbed from the air; the other, the water from the air, and in addition that given off by the skin. In this way the amount of water given off by 37.5 square centimeters of skin was determined. A number of blank experiments were made to test the accuracy of our method. The difference between the two sets of tubes in the blank experiments never was as great as 1 mg.

We preferred the method described to the one employed by Galeotti and Macri.[4] Their apparatus consists of a small metal box with a sliding lid and with calcium chlorid fragments fastened to the inner surface. The box is weighed and placed on the skin and the lid withdrawn. After fifteen minutes the lid is replaced and the box again weighed. The gain in weight determines the insensible perspiration. This method is open to the objection that the apparatus is really a desiccator and, in addition, all of the carbon dioxid given off by the skin is included in the determination.

In selecting the part of the skin to be studied the chest was decided on because of the convenience of applying the metal box over this rather large and relatively flat surface; this portion of the body is also relatively immobile in the infant, in whom the abdominal type of respiration prevails. The arrangement of our experiments gives figures for only a limited area of skin. Galeotti and Macri[4] and Loewy[2] have shown that different areas of skin give off different

4. Galeotti and Macri: Biochem. Ztschr., 1914, **67**, 472.

amounts of water vapor. We cannot, therefore, with our method obtain any accurate data with reference to the total loss of water by insensible perspiration through the skin, but we can obtain information about the variations of a given area and about some factors influencing the insensible perspiration in this area.

RATE OF VENTILATION

In choosing the rate of air flow it was desired to maintain a sufficient ventilation to prevent an accumulation of moisture in the metal box overlying the skin and yet avoid a cooling effect. For our first determinations we used an air flow of 7 liters per hour. In this way the air in the box was renewed 41.5 times per hour. Later some experiments were made to see what effect a more rapid rate of ventilation would have. These determinations were made on an adult, as it is of importance that the subject be quiet during the observations. The subject was seated and wore ordinary indoor clothing. The chest

TABLE 1.—INFLUENCE OF VARIOUS RATES OF VENTILATION

No.	Room Temp., C.	Rate	No. of Renewals per Hr.	Gm. H_2O per 37.5 Sq. Cm.	Gm. H_2O* per Sq. dm. per Hr.
1	19	7 L. per 60 min.	41.5	0.0137	0.0365
		14 L. per 60 min.	83.0	0.0204	0.0544
2	20	7 L. per 60 min.	41.5	0.0124	0.0331
		14 L. per 60 min.	83.0	0.0354	0.0944
3	..	7 L. per 60 min.	41.5	0.0164	0.0437
		14 L. per 60 min.	83.0	0.0247	0.0659
4	18	7 L. per 60 min.	41.5	0.0083	0.0221
		14 L. per 60 min.	83.0	0.0112	0.0299
5	21	7 L. per 43 min.	58.0	0.0014	0.0052
		14 L. per 43 min.	116.0	0.0032	0.0130
6	23	7 L. per 43 min.	58.0	0.0047	0.0175
		14 L. per 43 min.	116.0	0.0169	0.0629
7	18.5	14 L. per 60 min.	83.0	0.0252	0.0672
		21 L. per 60 min.	124.5	0.0189	0.0504
8	19.5	14 L. per 53 min.	93.9	0.0356	0.1075
		28 L. per 53 min.	187.8	0.0320	0.0966
9	20	14 L. per 43 min.	116.0	0.0035	0.0130
		21 L. per 43 min.	173.6	0.0064	0.0238
10	20	14 L. per 43 min.	116.0	0.0062	0.0231
		21 L. per 43 min.	173.6	0.0085	0.0343
11	20	21 L. per 60 min.	124.5	0.0472	0.1260
		28 L. per 60 min.	166.0	0.0285	0.0760
12	20	21 L. per 43 min.	173.6	0.0097	0.0360
		28 L. per 43 min.	231.5	0.0095	0.0353
13	20	21 L. per 43 min.	173.6	0.0106	0.0394
		28 L. per 43 min.	231.5	0.0097	0.0360

* The value in grams of water per square decimeter per hour in all of our tables are given for convenience of comparison with the figures of other observers.

was uncovered sufficiently to place the boxes on the skin. Each experiment consisted of two determinations following one another with just enough time intervening for weighing the calcium chlorid tubes. Deductions can, of course, be made only from such successive determinations, as it has been shown by Loewy[2] that the amount of insensible perspiration may vary considerably in the same individual on successive days under approximately similar conditions of temperature and humidity, a fact also very well illustrated in our observations.

It is seen that an increase in the rate of ventilation up to a certain point is accompanied by an increase of the values for insensible perspiration. When the rate is increased beyond this, there is not only no further increase, but even a decrease. A vasoconstriction in consequence of cooling suggests itself as a plausible explanation for this decrease. It may be mentioned that Loewy[2] has shown a definite decrease of the insensible perspiration on cooling the skin surface.

INSENSIBLE PERSPIRATION OF THE NORMAL INFANT

Table 2 gives the results of determinations of insensible perspiration in convalescent and normal infants. In Nos. 1 to 3 the infants wore only cotton diapers and the rate of ventilation was 7 liters per hour. In Nos. 4 to 8 the babies wore cotton stockings, cotton undershirts and diapers. The undershirts were opened over the chest to allow the apparatus to come in contact with the skin. The rate of ventilation was 14 liters per forty minutes. Of the latter group, in Nos. 6c and 6d the child was restless. In 6e the child was fretful and cried at times. Nos. 7 and 8 give the results obtained from observations on the same infants serving for Nos. 2 and 3, but with the room temperatures from 5.5 to 7 degrees C. higher. The relative humidity was about the same in all observations, that is, around 30 per cent. With restlessness, with fretfulness and crying, and with increased room temperature relatively high figures were obtained for the insensible perspiration. One must be guarded in concluding that these factors actually determine an increase of insensible perspiration because of the variations which occur from day to day without any attributable cause, and the observations in the table were made on different dates. We have a number of other observations, however, which give additional evidence in support of such an effect. It happened rather frequently that an infant became fretful or cried in the course of experiments intended to test the effect of various factors on the insensible perspiration, such as the effect of clothing, etc. Such determinations, of course, had to be discarded, but invariably relatively high figures were obtained. In other words, whenever we had to deal with a restless, fretful or crying baby or whenever we had occasion to repeat an observation on any infant at a room temperature

decidedly higher than previously, the insensible perspiration was invariably greater. The sum total of our observations indicates strongly that the factors just discussed actually lead to an increase of the insensible perspiration.

TABLE 2.—BARE CHEST

A. Average Room Temperature

No.	Age, Mos.	Wt., Kg.	Rect. Temp., C.	Room Temp., C.	Rate of Ventilation	Gm. H_2O per 37.5 Sq. Cm.	Gm. H_2O per Sq. dm. per Hr.	Diagnosis	Remarks
1	4½	4	37	23.5	7 L. per 60 min.	0.0288	0.0768	Convalescent from gastro-enteritis	Quiet
2	4	4	37	23	7 L. per 60 min.	0.0262	0.0698	Convalescent from gastro-enteritis	Quiet
3a*	9	5	37	23	7 L. per 60 min.	0.0198	0.0510	Convalescent from atrophy	Quiet
3b	9	5	36.5	23	7 L. per 60 min.	0.0190	0.0506	Convalescent from atrophy	Quiet
4	7	6	36	21	14 L. per 40 min.	0.0252	0.1512	Convalescent from gastro-enteritis	Quiet
5	4	6	37	25	14 L. per 40 min.	0.0725	0.4350	Normal	Quiet
6a	10	8	37	24	14 L. per 40 min.	0.0390	0.2340	Normal	Quiet
6b	10	8	37.5	26	14 L. per 40 min.	0.0504	0.3024	Normal	Quiet
6c	10	8	37	25	14 L. per 40 min.	0.0637	0.3822	Normal	Somewhat restless
6d	10	8	37.5	24.5	14 L. per 40 min.	0.0681	0.4086	Normal	Somewhat restless
6e	10	8	37.5	26	14 L. per 40 min.	0.1325	0.7950	Normal	Very restless crying at times

B. High Room Temperature

7a	4	4	37	28.5	7 L. per 60 min.	0.0546	0.1430	Convalescent from gastro-enterit's	Quiet
7b	4	4	37	30	7 L. per 60 min.	0.0634	0.1610	Convalescent from gastro-enteritis	Quiet
8	9	5	37	29	7 L. per 60 min.	0.0356	0.0949	Convalescent from atrophy	Quiet

* In tables, letters following numerals indicate additional observations on the same individuals.

INFLUENCE OF CLOTHING

In attempting to determine what effect clothing has on the amount of water vapor given off to the surrounding air, we made determinations with the metal box placed on the clothing overlying the chest and followed these almost immediately with determinations on the

bare chest. The results obtained in these observations were quite variable.

In one adult, for instance, the amount of moisture given off through the clothing (which consisted of two layers of cotton clothing that had been worn for seven to eight hours) corresponded closely with the amount given off from the bare skin of the same region (Table 3A).

In another adult with similar clothing, which had been worn for eight hours, there were somewhat greater variations (Table 3B).

In a series of observations on infants where the clothing consisted of two layers of cotton material (the ordinary cotton hospital clothing,

TABLE 3.—SHOWING THE INFLUENCE OF CLOTHING

Adults

	No.	Surface	Hours Clothing on	Rate	Values	Subject and Date	Kind of Clothing
A	1	Over cloth	8	14 L. 1 hr.	0.0235	McC. 4/11/17	Two layers of cotton clothing
		Bare	....	14 L. 1 hr.	0.0246		
	2	Over cloth	7	14 L. 1 hr.	0.0185	McC. 4/12/17	Two layers of cotton clothing
		Bare	....	14 L. 1 hr.	0.0175		
	3	Over cloth	7	14 L. 1 hr.	0.0234	McC. 4/13/17	Two layers of cotton clothing
		Bare	....	14 L. 1 hr.	0.0231		
B	4	Over cloth	8	14 L. 40 min.	0.0127	S. 9/28/17	Two layers of cotton clothing
		Bare	....	14 L. 40 min.	0.0066		
	5	Over cloth	8	14 L. 40 min.	0.0082	S. 9/29/17	Two layers of cotton clothing
		Bare	....	14 L. 40 min.	0.0092		
	6	Over cloth	8	14 L. 40 min.	0.0286	S. 10/ 2/17	Two layers of cotton clothing
		Bare	....	14 L. 40 min.	0.0189		

Infants

	No.	Age, Mos.	Wt., Kg.	Rect. Temp., C.	Room Temp., C.	Chest	Gm. H_2O per 37.5 Sq. Cm.	Gm. H_2O per Sq. dm. per Hr.	Rate	Diagnosis	Remarks
C	1	11	10	39	23.5	Clothed	0.0361	0.1440	14 L. 40 min	Acute otitis media	Somewhat restless
						Bare	0.0304	0.1220	.....	.....	Quiet
	2a	8	4.5	37	23.5	Clothed	0.0826	0.3304	14 L. 40 min.	Convalescent from gastro-enteritis	Quiet
						Bare	0.0005	0.2420	.....	.....	Quiet
	2b	8	4.5	37	24.5	Clothed	0.0693	0.2772	14 L.	.....	Quiet
						Bare	0.0488	0.1952	40 min.	.....	Quiet
	2c	8	4.5	37	25.5	Clothed	0.1026	0.4104	14 L.	.....	Quiet
						Bare	0.0692	0.2768	40 min.	.....	Slightly fretful

worn for eight hours) there was usually somewhat more moisture given off from the clothed than from the bare chest (Table 3C).

The fact that the infants frequently became fretful, or the occurrence of slight regurgitations of stomach contents, etc., made it necessary to reject a considerable number of observations. The observations on the infant in No. 2, though she was much underweight, were selected to show the effect of clothing in the absence of restlessness and other disturbing factors.

It does not seem improbable that the greater amount of moisture given off from the clothed, as compared with the unclothed chest, where such was the case, can be accounted for by the increase of skin surface temperature[1] due to the clothing.

In order to determine whether the clothing (as used in Table 3B) itself might give up moisture, we made determinations by placing the metal box over the clothing which was lying on a glass plate. The accompanying Table 4 shows the very low values thus obtained.

TABLE 4.—Tests of Clothing Alone

No.	Surface	Rate	Values in Grams	Kind of Clothing
1	Over plate glass	14 L. 40 min.	0.0040	Two layers of cotton clothing as in Table 3B
2	Over plate glass	14 L. 40 min	0.0011	Two layers of cotton clothing as in Table 3B
3	Over plate glass	14 L. 40 min.	0.0019	Two layers of cotton clothing as in Table 3B
4	Over plate glass	14 L. 40 min.	0.0007	Two layers of cotton clothing as in Table 3B

It was desired, furthermore, to see how easily moisture passes through the clothing. A wire mesh was placed over a shallow vessel which was filled with water to within an inch of the top. Two layers of cotton clothing such as used in the experiments were spread on this mesh and the metal box placed over the clothing; then the determination was made of the amount of moisture given off in the first forty minutes. Thirty minutes after the completion of this determination (seventy minutes after the clothing was placed over the vessel) a similar determination was made. Table 5 shows the results of this experiment.

The metal box was placed on wire mesh over the vessel of water and a determination was made; then the two layers of clothing were placed on the mesh, the metal box placed over the clothing and another determination made. Table 6 shows the result.

TABLE 5.—TESTS OF CLOTHING PLACED OVER WATER

Surface	Hrs. Clothing on	Rate	Values	Kind of Clothing
Over dish of water	Immediately	14 L. 40 min.	0.0745	Two layers of cotton clothing as in Table 3B
Over dish of water	After 1 hour 10 min.	14 L. 40 min.	0.0733	Two layers of cotton clothing as in Table 3B

TABLE 6.—ANOTHER DETERMINATION OVER WATER WITH AND WITHOUT CLOTHING

Surface	Hrs. Clothing on	Rate	Values	Kind of Clothing
On wire mesh 1 in. above water; no clothing	.....	14 L. 40 min.	0.0430	
Same over clothing	Immediately	14 L. 40 min.	0.0389	Balbriggan undershirt and cotton shirt

From these observations it may be concluded that this particular clothing, when worn for a number of hours, is little if any bar to water vapor loss.

Whether or not the humidity of the room air exercises an influence we cannot say. Our data do not permit us to draw any conclusions and we therefore omitted figures for the relative humidity from our tables. Niemann[5] seems to be the only one attributing a marked effect of the humidity of the air on the insensible perspiration of water from lungs and skin, while Nuttall[6] maintains that a variation in the percentage of relative humidity of the air has very little effect. This question is by no means settled; it is of great importance, but must be left to special investigation.

ATROPHIC INFANTS

In some observations on atrophic infants we found higher values for insensible perspiration than those obtained on convalescents under approximately equal conditions of room temperature, humidity and rate of ventilation.

Niemann[5] had found the total water vapor loss (that of the skin and lungs together) greater in atrophic than in normal infants. This falls in line with the observations of Schlossmann,[7] Bahrdt and Edelstein,[8] and Murlin and Hoobler,[9] which show that the metabolism of

5. Niemann: Ergebn. der inn. Med. u. Kinderh., 1913, **11,** 32.
6. Nuttall: Arch. f. Hyg., 1895, **23,** 184.
7. Schlossmann: Ztschr. f. Kinderh., 1912-1913, **5,** 227.
8. Bahrdt and Edelstein: Festschrift, Dr. Otto Heubner, Berlin, 1913.
9. Murlin and Hoobler: Am. Jour. Dis. Child., 1915, **9,** 81.

atrophic infants proceeds at a higher level, and with the observations of McClure and Sauer[1] that atrophic infants may have a high surface temperature.

It is self-evident from the foregoing that we are as yet far from being able to assign to insensible perspiration of water from the skin of the infant the rôle it plays in the heat economy of the organism. There is no doubt that it cannot be neglected as a factor of heat elimination, and, what is perhaps of special significance, some of the data given indicate that this mechanism possesses a rather great degree of elasticity. It would seem adapted to replace some of the other means of heat elimination, if that became necessary, particularly in the non-perspiring infant.

TABLE 7.—Determinations in Atrophic Infants

No.	Age, Mos.	Wt., Kg.	Rect. Temp., C.	Room Temp., C.	Chest	Gm. H_2O per 37.5 Sq. Cm.	Gm. H_2O per Sq. dm. per Hr.	Rate	Diagnosis	Remarks
1	9	5.5	36.5	25.5	Bare	0.1284	0.3157	7 L. 60 min.	Severe atrophy	Quiet
2	2	2.5	36.0	22.0	Bare	0.0694	0.1850	7 L. 60 min.	Severe atrophy	Quiet
3a	6	3.5	35.5	23.0	Bare	0.0928	0.1474	7 L. 60 min.	Severe atrophy	Quiet
3b	6	3.5	36.0	24.0	Bare	0.0847	0.2258	7 L. 60 min.	Severe atrophy	Quiet

SUMMARY

In so far as determinations of the loss of water vapor from a restricted skin area permit of conclusions with regard to the loss of water vapor from the skin in toto, it appears:

1. The rate of ventilation has a decided effect on the amount of water vapor given off by the skin. This amount increases with the rate of ventilation up to a certain point, when it seems that a cooling effect prevents a further increase.

2. Cotton garments, such as used in our experiments, do not seem to offer any obstacle to the loss of water vapor from the skin; at least not when they have been in contact with the skin a number of hours.

3. Such factors as fretfulness, crying and increase in the room temperature increase the insensible perspiration of the infant.

4. The loss of water vapor from the skin of certain atrophic infants is relatively great.

5. The loss of water vapor from the skin seems sufficiently great to make it an important factor in the heat elimination of the infant. Furthermore, this mechanism of heat elimination seems to possess a great degree of elasticity.

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